Ague and Fever, by T Rowlandson, London, 1792

From Holländer, 1905, Die Karikatur und Satire in der Medizin, *published by F. Enke, Stuttgart*

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Man's Mastery of Malaria

By

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Respectfully dedicated to

JOHN DAVISON ROCKEFELLER

(1839–1937)

to his son

JOHN DAVISON ROCKEFELLER, JUNIOR

and to his grandson

JOHN DAVISON ROCKEFELLER, 3RD

who through their benefactions and
by their continued interest in the
well-being of mankind throughout the world
have assisted thousands of communities
to control disease-carrying mosquitoes
and to master
preventable afflictions

PREFACE

The Heath-Clark Bequest was given in 1929 to make possible an annual series of lectures under the auspices of the University of London It was stipulated in the Deed Trust that 'the general scope of the lectures to be given shall include the educational, cultural and humanistic aspects (as opposed to technical and manipulative training) of the History, Development and Progress of Preventive Medicine and Tropical Hygiene and their sanitary and social evolution both in temperate and tropical climates' When the invitation came to me, I naturally thought first of the history of malaria because the disease has been of prime interest to me for many years But I hesitated because the subject has already been so thoroughly publicized and I feared that what I might say would seem trite Then I realized that the developments in malaria control in recent years have been so tremendous that it would be difficult to be dull in the telling of the story of how man has at last mastered malaria

I hope that the title of these lectures is not misleading One should remember that the verb 'to master' means 'to overcome, defeat, reduce to subjection' So, to master malaria does not necessarily mean to eradicate it, nor should there be a connotation of freedom from further responsibility On the contrary, malaria certainly remains for many people a harmful reality, it still does immense economic, social, and physical damage Exactly how much malaria remains no one knows because the data reported are so inadequate, but on the basis of what I have seen and read, it seems to me safe to estimate that among the 2,500 millions of people in the world today, more than half live in potentially or actually malarious communities While probably no fewer than 160 millions today are enjoying the protection of modern malaria control, an amazing achievement, yet it seems a fair guess that in 1954 some 250 million persons will suffer attacks of malaria and that very likely 2½ million will die from its effects

Malaria will continue to constitute a problem for health officials of international agencies and of certain countries for some time to come. No, the verb 'to master' does not imply an end to the matter: rather it suggests that having prevailed over an opposing force one has assumed moral responsibility for keeping it under control.

The point is that malaria, after centuries of effort, is now universally controllable. Techniques are available and for most communities, even those least developed, the cost of malaria control is not beyond local means. In several instances, countries once highly malarious have succeeded in stopping the transmission of this disease during the past decade. Malaria is retreating with spectacular acceleration. Man is indeed master at last. But can he overcome stubborn terminal opposition? Can he consolidate and maintain his mastery? I consider it entirely possible but not easy, especially in view of the increasing likelihood that the anopheles mosquitoes that transmit malaria will join the growing band of insects that are able to resist modern residual insecticides such as DDT.

While keeping in mind the realities one can nevertheless be confident that malaria is well on its way towards oblivion. Already as a malariologist, I feel premonitory twinges of lonesomeness, and in my own organization I am now a sort of 'last survivor'. So perhaps it is fitting that I should take this backward glance at the fascinating pages of malaria history.

I believe in the importance of historical studies. As Oliver Wendell Holmes once said: 'The debris of broken systems and exploded dogmas form a great mound, a Monte Testaccio of the shards and remnants of old vessels which once held human beliefs. If you take the trouble to climb to the top of it, you will widen your horizon, and in these days of specialized knowledge your horizon is not likely to be any too wide.'

But I do not present these lectures as more than a retrospect of the highway that has led, to quote the editor of *The Lancet*, 'from mystery to mastery'. Some idea of the fact that the following story is indeed only a brief survey,

not the whole account, may be had by consulting the first Index-Catalogue of the Library of the Surgeon General's Office, U S Army, dated 1883 Here, under the heading 'Fever—Malarial' in volume iv, were listed over 700 books and many hundreds of articles in journals, mostly nineteenth century Add to these sources the hundreds of books and papers listed under 'Malaria and Malarial Diseases' in volume viii and one sees an astounding pile of untapped material already accumulated seventy years ago Since then the literature has increased enormously I fully realize that I have not been able to go far beyond the bare outlines of the subject

Had I set out to write a definitive history of malaria, I would have ended it at or some time before the Second World War It is, of course, too soon to evaluate with confidence the developments of the past fifteen years But in this retrospect it seemed desirable to embrace the full length of the road, including that exciting part most recently travelled I would be surprised as we go forward, if perspective did not indicate changed appearances in this area closest to us and reveal defects of interpretation and proportion in the following story

But, limited though they are, these studies have repaid me for the effort As the great medical historian Baas said so well, history offers to him who studies it a 'measure for the just and well-founded criticism of the doings of his own time, places in his hand the thread by which he unites past conditions and efforts with those of the present, and sets before him the mirror in which he may observe and compare the past and present, in order to draw therefrom well-grounded conclusions for the future'

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SECTION I

THE UNFOLDING OF MALARIA AETIOLOGY

THIS is not a history of malaria Here is simply a retrospect, a looking back at some facets, individuals, and ideas prominent in the long unfolding or opening up of what had been hidden from view Somewhere it is written that the best history resembles Rembrandt's paintings: certain selected aspects vivid, the rest in shadow or unseen One agrees and has tried to spot-light rather than to flood-light So, too, the approach is optimistic and not in the spirit of Hegel's cynical remark that, 'The one thing one learns from history is that nobody ever learns anything from history' It is true that some lessons come only through personal experience Yet, historical study does add meaning and interest, it does dispel illusion Ronald Ross used to say that 'an historical introduction is always necessary to give coherence to ideas' Quoting Rowse of Oxford, 'History is part of the self-awareness of our environment'

As one reads again various accounts of the long struggle against malaria, now flowing so dramatically in man's favour, it appears that there has been no steady triumphal march Rather, as suggested by Conant's simile, the happenings resemble those of modern warfare advance objectives wished for, reconnoitred, attacked, boldly seized, precariously held, and painstakingly consolidated

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SPECULATIONS

Prehistoric Beginnings

One must go far back into prehistoric time for the origins of malaria. Indeed, one might begin by crystal-gazing into a ball of translucent amber. Embedded in this fossil sphere is a mosquito caught by liquid resin in the Age of Reptiles, long before man existed. Or one might examine a flake of rock from the Insect Bed of the Isle of Wight, looking for a petrified mosquito, drowned and buried in the silt of its breeding-place, millions of years ago. These rare souvenirs include *Culex*, *Aedes*, and *Mansonia* mosquitoes and one may therefore assume that the malaria vector tribe of *Anophelini* was also present in those early days because, morphologically, it is an even more primitive stem than the specimens so far discovered.

Accordingly, we believe that when man appeared, mosquitoes were already an ancient form of life, with needles sharpened and adapted to the procurement of vertebrate blood. Very likely, too, the mosquito had already formed its close partnership with the protozoan that is the cause of malaria. In what vertebrate the plasmodia first existed as parasites we do not know, but it seems likely that they were not long, as time is measured, in adapting their metabolism to the chemistry of man's cells and fluids. One assumes, with Sigerist, that disease is as old as life.

Fossil bacteria are found in early rocks, in petrified fishes, and in the teeth and jaws of fossil vertebrates. In Egyptian mummies there are embalmed bacteria which seem to be those of tuberculosis and of plague. Calcified eggs of *Schistosoma haematobium*, the worm parasite that causes schistosomiasis, and enlarged spleens possibly of malaria, have also been found in mummies dating back 3,000 years. In fact, paleopathological studies seem to demonstrate

that disease has occurred during thousands of years in the same basic forms Quoting Sigerist,

> Whether the bones were human or animal bones, whether they were neolithic or paleolithic, eocene or permian, we always found the same type of disease, disturbance of development and of metabolism, inflammation, and repair, new growth, and true tumors the same forms of disease that we can observe today

Certain chimpanzees in Central Africa are naturally infected with what appears to be the identical *Plasmodium malariae* now found in man This quartan parasite is perhaps the oldest species of plasmodium in the scale of evolution and may have been the first to invade man Since parasitic infections abound in all the primates, it is not unreasonable to believe that early man suffered likewise

> Bone of our bone, and flesh of our flesh, are these half brutish prehistoric brothers Girdled about with the immense darkness of this mysterious universe even as we are they were born and died, suffered and struggled
>
> William James—'Human Immortality'

No one can know how an infectious fever like malaria originated nor has any one witnessed the birth of a new protozoal disease But one takes no great liberty with historical truth in assuming that prehistoric man, at least in some of the warmer regions, must have experienced malarial chills and fevers

Pre-Grecian and Oriental Notions

Although references are relatively few and unsatisfactory, it seems reasonable to suppose that in pre-Grecian times malaria was not a serious problem in Egypt and the Near East but was highly prevalent in parts of Mesopotamia, India, and south China The disease may have been rare in the Nile delta but more common in the upper valley Egyptologists state that possibly the word AAT, found among the inscriptions of the temple of Denderah, meant malaria

Allusions to fevers, some clearly intermittent in character, are fairly common in Babylo-Assyrian medical lore

Additional interest attaches to the fact that Nergal, the Babylonian god of pestilence, was depicted in the form of an insect, possibly signifying that even in those days some priests thought that flies or mosquitoes took part in the transmission of disease Probably man has always considered many insects to be harmful, not because of remote effects such as malaria, but because of the often painful reaction to a sting Perhaps such common local injuries were sufficient to induce the Babylonians to represent their pestilence-causing god Nergal as a two-winged fly, and the Canaanites to follow with Baal-zebub, the 'god of flies' and 'prince of devils' Certainly, the house-fly, the mosquito, and the sand-fly greatly plagued and still afflict the people of those areas

Ancient Jewish ideas of aetiology resembled those of Babylonia Demons and demonic possession, for example, are often mentioned in the Talmud There appears to have been some notion of the infectiousness of certain fevers, for we read that it was customary to blow the horn (*shofar*) when three cases had been reported Malaria doubtless was endemic in Palestine But Short, in his survey of health and healing in the Old and New Testaments, records surprisingly few references to diseases that can be assumed to have been malaria In Leviticus xxvi 16, 'the burning ague' or *qaddahath* in Hebrew, simply referred to as 'fever' in the Revised Version, was perhaps mostly malaria The word in Deuteronomy xxviii 22, translated as 'inflammation', is *dalleqeth* in Hebrew which in the old Greek version, or Septuagint, is rendered as intermittent fever The case of the Shunammite lad in 2 Kings iv 14–37 may have been cerebral malaria and finally, the 'great fever' of which Peter's mother-in-law was healed (Luke iv 38–39) seems likely to have been malarial

There was a voluminous medical literature in ancient India, the best-known works being the *Charaka Samhitā* and the *Śusruta Samhitā*, compilations with added observations by the two famous sages Charaka and Śuśruta One of the four *Vedas* of the Hindus is the Arthavana, of which the Ayurveda is a part and the latter constitutes a chief

source of Vedic medical teaching In it malaria is referred to as a most dreaded affliction, the 'King of Diseases' Usually, this malady was attributed to the anger of the god Shiva The records say that it prevailed largely in the autumn Symptoms are described as alternating between hot and cold fever returning daily or every third day Tertian and quartan fevers were clinically well defined and one has little doubt that they were in fact malaria There is a paragraph that describes a 'splenic belly' with 'an enlarged spleen which distends the left side, is as hard as a stone, and is arched like the back of a turtle'

According to Raina, the early Ayurvedic authors Charaka and Suśruta both noted the periodicity of malaria The first wrote of planted seeds, some taking a day, some two, and others three days to grow When developed they invaded the whole body and, not being opposed by contrary forces, they caused fevers Śusruta, on the other hand, said the phenomenon resembled the ebb and flow of the tide

Malaria was well known in China many centuries before the Christian era The Chinese differentiated tertian from quartan fevers and noted the enlarged spleen The demonic origin of this disease, as of others, was widely believed For example, there is a reference in Chinese mythology to three demons said to be responsible for the characteristic headache, chill, and fever of malaria The first demon was equipped with a hammer, the second with a pail of cold water, and the third with a stove

Ancient Chinese physicians differentiated varieties of intermittent fevers and noted the associated 'ague-cake' There is a 'Song of the Spleen' in old Chinese medical literature which seems to refer to the enlargement due to malaria The greatest Chinese physician of the second century was Chang Chi, who wrote a treatise on fevers which was exceedingly popular and remained so until recent times Some Chinese physicians considered that most bodily ills were due to disturbed relationships between the vital principles *yang* and *yin* Disorders of the *yang*, or positive factor, caused fevers, of the *yin*, or negative factor, resulted in chills

The oldest existing medical text in Japan is the *Ishinho*, written in 982 and derived largely from Chinese sources In it several types of intermittent fevers are described, including hot and cold varieties, a chronic form, one attributed to miasmata, and one in which the fever recurred regularly every second or third day

All in all, pre-Grecian and Oriental aetiology was largely compounded of the mysterious influence of assorted gods, the black magic of wizards, demons of many varieties, the power of fetishes, the evil eye of enemies, the offended spirits of dead men and animals, or even of plants As the modern hypochondriac apprehensively visualizes the entry into his organs of malaria parasites that he has heard about but never seen, so primitive peoples worried about pestiferous demons and spirits in earth, air, and water, ready to penetrate their bodies in obedience to malicious command or capricious whim Like the savage or the superstitious layman today, ancient man regarded disease as supernatural and he developed his ideas of aetiology, therapy, and prevention on that premise No doubt the sudden onset of chills and fever of malaria made this disease particularly liable to seem to be the work of demons or spiteful spirits

Hippocrates the First Malariologist

Out of the night, out of the blinding night
The beacon flashes, hail, beloved light of Greece
Lucretius, Book III

Fevers were common in Greece, apparently from earliest times One of the first references is in the *Iliad* of Homer, dating back about a thousand years before Christ Here there was recognition of seasonal variation in the incidence of fevers Homer wrote

Not half so dreadful rises to the sight,
Through the thick gloom of some tempestuous night,
Orion's dog (the year when autumn weighs),
And o'er the feeble stars exerts his rays,
Terrific glory! for his burning breath
Taints the red air with fevers, plagues, and death
(Book XXII Pope's translation, p 99)

Prior to Hippocrates, there were in ancient Greece physicians like Aesculapius and his sons, Podalirius and Machaon, there were priest-guardians of the Aesculapian shrines who often practised healing, there were philosophers like Pythagoras who did not hesitate to treat disease and who emphasized diet, music, and mystical numbers as logical in view of the aetiology they postulated, there were others, like Democedes, who was one of the earliest public medical officers on record, first in Aegina, then in Athens, and finally in Samos, and there were the gymnasiarchs, like Herodicus of Selymbria who enthusiastically insisted that not only sprains and dislocations but all diseases, including fevers, arose in much the same way and should be treated by appropriate exercises

In Sicily there was the Greek philosopher Empedocles of Agrigentum, who introduced an important new aetiological note in his poem 'On Nature' Quoting Withington's translation

Listen first, while I sing the four fold root of creation,
Fire and water, and earth, and the boundless height of the aether,
For therefrom is begotten what is what was, and what shall be

Substituting air for aether, here is the doctrine of the *four elements* Adding the *four qualities*—heat, cold, moisture, dryness, and the *four humours*—blood, phlegm, black bile, yellow bile, one has the basis on which Hippocrates and his Greek colleagues, Romans, Byzantines, indeed, physicians down through the Middle Ages and later, discussed the pathogenesis of malaria and many other diseases Illnesses originated in disturbances of balance between the humours, the qualities, and the elements, sometimes thought due to supernatural agencies

Hippocrates of Cos (460–377 B C) was not bound by supernaturalism He taught that no disease comes from the gods, nor does one more than another Each disease has its own natural and manifest cause The quotidian, tertian, and quartan fevers, he said, are no more and no less divine than epilepsy, at that time called 'The Sacred Disease'

Hippocrates has often been called 'The Father of Medicine', although he dates about half-way between Imhotep,

the great Egyptian physician, and modern times He might also be called with some justification the first malariologist since no one before him or for many years afterwards so clearly and fully described the intermittent fevers Quotidian, tertian, and quartan fevers were named as distinct from continued Their periodicity and several characteristic features, such as headache and chills, were discussed by Hippocrates and he vividly outlined the physical characteristics of children afflicted by chronic malaria He also noted the phenomenon of exacerbations or relapses Hippocrates was acquainted with seasonal and topographical variations in the distribution of paludism and he recognized an association between marshes and fevers He commented that those who drank the stagnant marsh water 'have always large, stiff spleens and hard, thin, hot stomachs, while their shoulders, collar bones and faces are emaciated, the fact is that their flesh dissolves to feed their spleens'

Further on in *Airs Waters Places*, the authorship of which is not disputed, Hippocrates wrote 'Should there be rivers in the land, which drain off from the ground the stagnant water and the rain water, these [the people] will be healthy and bright But if there be no rivers, and the water that the people drink be marshy, stagnant, and fenny, the physique of the people must show protruding bellies and enlarged spleens' This treatise *Airs Waters Places* is the earliest known essay on the influence of physical environment upon health and disease It described effects upon health of the seasons, winds, quality and composition of waters, nature of soils, and location of residence In effect it emphasized the importance of what epidemiologists now call regional surveys

Hippocrates was opposed to the meaningless manipulations, snake charms and conjurations of priests and astrologers He had a sane attitude towards medicine, avoiding words divorced from things, emphasizing the importance of the natural history of disease, the need to observe as well as to theorize He was more than a clinician, for he had great interest in preventing disease

No evidence exists that Hippocrates, although much

impressed by the effects of climate and of marshes on the health of men, ever guessed or speculated about such intermediaries as insects or animalculae in the causation of disease nor does it appear that he had any ideas about specific marsh miasmata. But he was keen enough to observe the correlation between environment and disease and to see in airs, waters, and places, the origin of malaria. Today there are physicians in tropical areas, yes in the temperate zone, too, with eyes so firmly fixed to microscope and on prescription forms that they fail to see these airs and waters and places. They neglect environmental sanitation.

There are clear references to the intermittent fevers in the writings of Sophocles, Aristophanes, Plato, Aristotle, and Demosthenes. Malaria appears to have been a much more common affliction in Greece after about 400 B.C. In A.D. 2–3, Aretaeus of Cappadocia noted, as had Hippocrates before him, an aetiological relationship between marshes and splenic enlargement.

Roman seeds

There is no evidence that malaria was a public health problem among the ancient Etruscans who inhabited the Roman Campagna before the days of the Republic. But it seems certain that this disease followed closely on the period of Etruscan decadence, if indeed it was not a factor in the decline. Undoubtedly malaria was common in Italy after about 200 B.C. and it was a prominent feature of the society of the Roman Republic. It became even more serious during the period of the empire, preventing the cultivation of food-crops throughout the Campagna and depopulating several areas. So intense was malaria in ancient Rome that there were temples dedicated to the goddess *Febris*, who was addressed variously as *Febris diva*, *Febris sancta*, and *Febris magna*. She was worshipped on the Palatine Hill and was thought to govern both the tertian and quartan fevers. Sambon has referred to 'the great, the mighty, the holy' *Dea Febris*, goddess of malaria, as 'a hairless old hag with prominent belly and swollen veins'. The Romans, although a practical people with substantial sanitary achievements,

yet were superstitious and certainly did not have the Greek medical objectivity Quoting Durant, 'the grandeur that was Rome was pomp of power rather than light of thought'.

Native Roman medicine prior to the arrival of the Greeks did not amount to much The common belief was that all diseases came from the gods and were to be arrested or averted by prayer and sacrifice The Etruscans contributed some ideas of magic which after 200 B C were counterbalanced gradually by more rational Greek ideas by way of Sicily and south Italy But prominent Romans had no liking at first for Greeks or Greek medicine Cato the Censor and Pliny the Elder, for example, were especially bitter in their comments Yet, it is interesting to realize, there is much truth in Withington's statement that everything worthy of the name of Medicine was Greek, from Hippocrates to Harvey, whether found in Alexandria, Rome, Baghdad, Salerno, or Paris

There were several clear descriptions of malaria in Roman medical literature For example, Celsus, a Roman aristocrat who most likely was not a practitioner of medicine, wrote about fever in his famous *De Medicina*, around A D 130, as follows (III 3 1–5)

Of fevers, one is quotidian, another tertian, a third quartan At times certain fevers recur in even longer cycles, but that is seldom

Now quartan fevers have the simpler characteristics Nearly always they begin with shivering, then heat breaks out, and the fever having ended, there are two days free, thus on the fourth day it recurs

But of tertian fevers there are two classes The one, beginning and desisting in the same way as quartan, has merely this distinction, that it affords one day free, and recurs on the third day The other is far more pernicious, and it does indeed recur on the third day, yet out of forty-eight hours, about thirty six, sometimes less, sometimes more, are in fact occupied by the paroxysm, nor does the fever entirely cease in the remission, but only becomes less violent This class most practitioners term *hemitrition*

Quotidian fevers, however, vary and have many forms For some begin straightaway with a feeling of heat, others of chill, others with shivering I call it a chill when the extremities become cold, shivering

when the whole body shakes Again, some desist so that complete freedom follows, others so that there is some diminution of fever, yet none the less some remnants persist until the onset of the next paroxysm, and others often run together so that there is little or no remission, but the attacks are continuous Again some have a vehement hot stage, others a bearable one, some are every day equal, others unequal, and the paroxysm in turn slighter one day, more severe another some recur at the same time the day following, some earlier or later, some take up a day and a night with the paroxysm and the remission, some less, others more, some set up sweating as they remit, others do not, and in some freedom is arrived at through sweating, in others the body is only made the weaker But the paroxysms also occur sometimes once on any one day, sometimes twice or more often Hence it often comes about that daily there are several paroxysms and remissions, yet so that each corresponds to one which has preceded it But at times the paroxysms also become so confused together that neither their durations nor intermissions can be observed (Translation of W G Spencer)

Here, in spite of some difficulty with the quotidians, there is certainly a recognizable description of malaria, stemming, of course, from Hippocrates

During the second century, that very remarkable physician, author, and teacher, Claudius Galenus established an authority in medicine that held powerful sway for 1,500 years Among a wide diversity of anatomical, pharmacological, medical, and surgical subjects, Galen, of course, discussed the intermittent fevers He believed that tertian fevers followed agitation of yellow bile, quartan of black bile, and quotidian of phlegm He described the clinical symptoms of the malarial fevers quite clearly

Horace, Lucilius, Lucretius, Juvenal, Martial, Tacitus, and Terence all mentioned the intermittent fevers as though well acquainted with them Pliny also discussed malaria with considerable understanding of the periodicity, the large spleen, and the relapses Cicero and Seneca both commented that paludism had depopulated certain districts of the Campagna

Many references make it certain that the Romans looked upon marshes as a source of disease Cato (234–149 B C), for example, commented on this subject Perhaps the most

notable passage was penned by Marcus Terentius Varro (116–27 B C) in *Rerum Rusticarum* His wife Fundania had bought a country estate which she wanted to farm to advantage and, at her request, Varro prepared detailed instructions In his foreword he said, 'My dear Fundania, if I had leisure I would give a better form to this treatise As I have not, I will do what a man may who has to bear in mind the need of haste Man is a bubble, they say, in which case the proverb must be more true of an old man And I am in my eightieth year, which warns me to pack up my baggage in readiness to journey out of this world' Nevertheless, Varro found time to prepare a practical handbook that was a classic and that he hoped would encourage his fellow countrymen to go back to the 'divine country' to that life 'which is not only the most ancient, but the best of all' Living in the neighbourhood of malarious Cassino, he clearly recognized the advantages of a good farm site Among other points, he wrote (I 12 ii), 'Note also if there be any swampy ground both for the reasons given above, and because certain minute animals, invisible to the eye, breed there, and, borne by the air, reach the inside of the body by way of the mouth and nose, and cause diseases which are difficult to be rid of' Varro then quoted his father-in-law, C Fundanius, as asking 'What shall I do to escape malaria, if I am left an estate of such a kind?' A friend, Agrius, responds 'Why even I can answer that question You must sell it for as many pence as you can get, or if you can't sell it you must quit it' (Translations of Storr-Best)

Also in the first century before Christ, Vitruvius, the Roman architect and engineer, wrote that the vicinity of a marsh should be avoided when building a house because, when the morning airs reach the house at sunrise, the mists of the marshes arrive with them, and the wind, mixed with these vapours, spreads the poisonous exhalations of the creatures inhabiting the marshes, and so makes the place pestilential

Lucius Junius Moderatus Columella (*c* 3 B C–A D 65) was probably acquainted with the writings of Varro and he

commented on marshes in a similar manner Quoting Columella, *Res Rustica* (Book I, v 6)

And neither should there be any marshland near the buildings and no military highway adjoining, for the former throws off a baneful stench in hot weather and breeds insects armed with annoying stings, which attack us in dense swarms, then, too it sends forth plagues of swimming and crawling things deprived of their winter moisture and infected with poison by the mud and decaying filth, from which are often contracted mysterious diseases whose causes are even beyond the understanding of physicians, and at every season of the year rust and dampness play havoc with farm implements and equipment, and with unstored and stored produce, the highway, moreover, impairs an estate through the depredations of passing travellers and the constant entertainment of those who turn in for lodging (Translation of H B Ash)

In a preceding passage of this same *Res Rustica* (Book I, v 3) Columella wrote

Worst of all is swamp water which creeps along with sluggish flow and water that always remains stagnant in a swamp is laden with death But this same water harmful though its nature is, is purified by the rains of the winter season and loses its virulence from this fact water from the heavens is known to be most healthful as it even washes away the pollution of poisonous water, and we have stated that this is the most approved for drinking

Another agriculturist, Palladius in the fourth century, advised that marshes were by all means to be avoided because they engendered pestilence and harmful animals Obviously, as Garrison and others have remarked, the Romans from the second century before Christ onwards, believed that marshes might be a source of ill health True, Columella and others, did not specifically point to intermittent fevers but in view of their general prevalence, in the place and season concerned, it is reasonable to suppose that these fevers were among the 'mysterious diseases' thought to originate in swamps

Finally, we mention a note by one of the atomists, Lucretius Carus (*c* 95–55 B C) in his *De Rerum Natura*, not written in special reference to any one disease It will be recalled that this Epicurean believed that knowledge did not

stem from mere inspiration. Things are what our senses tell us they are, or what they would appear to be if our senses were more acute. On this basis Lucretius wrote: 'I will now explain the nature of epidemics. . . . I have already shown that there are certain atoms or seeds of many substances that are helpful to our life, and there must also be many others flying about that are pestiferous and poisonous, conducive to death and disease.' Here again is the Greek atomic theory, invented by Leucippos of Miletus (*fl.* 450 B.C.), expounded by Democritus of Abdera in Thrace (460–356 B.C.), revived by Epicurus of Samos (341–270 B.C.), and publicized by Lucretius as part of his remarkable fight against superstition. This early atomic theory must not, of course, be equated with that of Dalton in the nineteenth century. Not at all, but none the less it should not be neglected. As Sarton has said, this theory of the atomists remained an intellectual stimulant for centuries. I believe it can be shown to have had a very definite influence in the development of ideas about the aetiology of malaria.

Middle Ages

Crombie says that, 'Perhaps of all the practical arts of the Middle Ages, medicine is the one in which hand and mind, experience and reason, combined to produce the most striking results.' While there do not appear to have been notable advances specifically in malariology yet this subject did share in the benefits from significant progress during the so-called 'Dark Ages'.

After the decay of the Roman Empire, folk-medicine for a time was especially popular. There was some tendency to go forward from the hocus-pocus of supernatural aetiology to more natural explanations. But the latter were usually a confused tangle of stellar, lunar, and planetary legends. Epidemics of malaria, and of other diseases, were explained as being the result of revolving planets, currents of starlight, blazing comets, telluric changes, terrestrial perturbations, baneful commotions of the atmosphere, mephitic vapours, febrific effluvia, vegeto-animal exhalations, marsh miasmata, and the like.

Of course, the balderdash of clinical and preventive practice of the past seemed logical to those who relied on it. Ignorance does not necessarily imply stupidity. So we do not scoff at the early mystical mumbling of magicians and the prophylactic praying of priests, or at the groping for cosmic forces in the aetiology of disease. Superstitions, 'things standing over', still have widespread vogue and a surprisingly large portion of the world's people today has but a conjurer's notion of how to prevent malaria.

A marked revival in Western medicine began at Salerno in the eleventh century. Latin translations of Hippocrates, Galen, and Dioscorides became available. Arab, Jewish, Nestorian, and Persian scholars had translated into their languages several of the early medical texts, sometimes corrupting them but more often inserting some of their own wise observations. Now these basic treatises as well as those of Avicenna, Isaac Israeli (a classic on fevers), Rhazes, and others, became accessible in Latin. Thus Greek and Eastern teaching spread in the West. By the twelfth century, Montpellier had superseded Salerno, and in the thirteenth-century it was joined by the medical schools of Bologna, Padua, and Paris. In these centres of learning, malaria was one of the principal diseases to come under close study and observation. The fact that, beginning with Taddeo Alderotti in Bologna, it became customary for leading teachers of medicine to write *consilia*, i.e. case-histories (a practice that seems to have been limited to Hippocrates and Rhazes previously) greatly advanced the understanding of some of the prevailing illnesses.

The Middle Ages and early Renaissance also produced some instruments of immense value to malariology and medicine in general. For example, the clinical thermometer was first devised by Santorio Santorii (1561–1636) at Padua. Obviously, physicians could thereafter measure and study the fevers of malaria and of other diseases much more intelligently. So, too, the physician's eyesight was tremendously aided by the microscope, an instrument fundamental in malaria investigations. As Robert Hooke wrote in his *Micrographia* (1665), by the use of such tools as the

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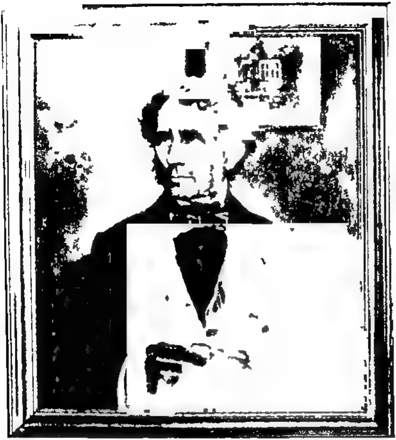


FIG 1 Daniel Drake, 20 October 1785—5 November 1852 of whom Osler said In many ways Daniel Drake is the most unique figure in the history of American Medicine Drake travelled over 30 000 miles to make the personal studies he thought essential in preparing his classic treatise on the diseases of the Interior Valley of North America among which malaria was one of the most prominent at the time

Photograph used by courtesy of Dr Emmet F Horine of Brooks Kentucky owner of the copyright

Tafel IX.

Die Pigmentleber. Melanämie und Folgen derselben für die Leber. Verhalten der Leber bei Intermittens comitata.

Fig. 1. Durchschnitt einer melanämischen Leber. Das Organ hat ein chocoladefarbiges Aussehen; auf der schwärzlich grauen Grundfläche bemerkt man braunrothe Figuren, die etwas hyperämischen und gallenfarbstoffreichen Gebiete der V. hepaticae.

Fig. 2. Pigmentstoffe aus der Pfortader.

- a. Aus dem Stamme derselben entnommen, schwarz pigmentirtes Gefässepithel, zum Theil mit deutlichem Kern von spindelförmiger runder Gestalt, [illegible] braunroth gefärbte Form, normale Blutkörperchen.
- a'. Aus der V. lienalis.
- b. Cylindrisch geformte pigmenthaltige Scholle.
- c. Grössere stark pigmentirte Gerinnsel aus der V. lienalis.

Fig. 3. Feiner Schnitt einer gekochten und mit Kalilauge behandelten Leber. Die Pigmentstoffe liegen in den Capillaren zwischen den Leberzellen bis zur V. centralis, [illegible]

Fig. 4. Feiner Schnitt von einer andren in derselben Weise behandelten Leber (Krocker) [illegible] Die Pigmentstoffe haben sich grösstentheils in den Vv. interlobularibus festgesetzt, sind spärlich in die Gefässe der Läppchen eingedrungen.

Fig. 5. Injection einer melanämischen Leber zehn Wochen nach Ablauf der Febr. intermittens. Die gelb injicirten Pfortaderäste, welche bis zu ihrem Eintritt in die Läppchen erweitert sind [illegible] zum Theil [illegible] kolbig; ihre capilläre Ausbreitung lässt sich nur unvollkommen injiciren, dieselbe ist theilweise mit Pigment gefüllt und obliterirt. Die Capillaren der Lebervene, roth injicirt, zeigen nichts Abnormes, die Leberzellen sind mit Gallenfarbstoff imprägnirt.

2 A

Fig. 2. Photograph of Plate IX in Frerichs's Atlas, 1858, showing pigment found in certain tissues from a fatal case of intermittent fever. A. The descriptive text. B. Plate IX. C. Enlargement of drawings that probably depict malaria parasites, unrecognized as such.

Courtesy of the Zurich Medical Library and the Library of the World Health Organization

2 C

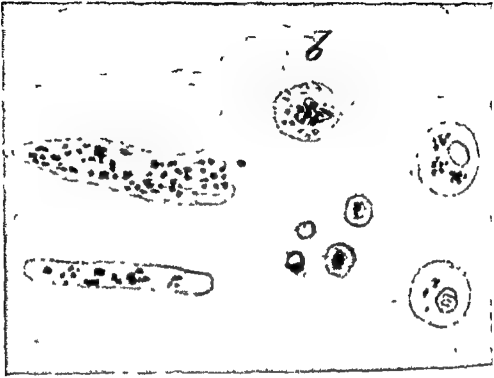
mental Italian studies of plasmodia and of mosquito vectors were published between 1880 and 1900 by the society.

Going back to the Middle Ages, one can probably say with justice that from the thirteenth century onwards, biology took its place as a science, combining observation with natural explanation, a development that contributed fundamentally to the growth of malariology.

Thus we must not underrate the Middle Ages. Those who produced the decimal system, the mariner's compass, the great cathedrals, the French *Chansons*, German *Minnesanger*, the *Magna Carta*, parliamentary government, and above all, the universities, command our profound admiration. The Dark Ages were indeed not uniformly black. To one who lived during the thousand years or so from the fifth to the fifteenth century our modern term, 'Dark Ages' would no doubt have seemed ridiculous. We recall that Abelard's followers called themselves *moderni* and that the Bishop of Exeter in 1287 termed his century, *moderni tempores*! In the words of Henry Adams, the world at that time may have been rough but it was not stupid; one would add, at least, to no greater extent than it is today.

Malaria Acquires its Name

By the seventeenth century, the 'Roman Airs' were notorious in many parts of the malarious world. There was well nigh universal belief in an aetiological relationship between swamps and intermittent fevers. It was widely held that these agues were due to miasmata, to disease-producing substances that invaded man from outside, and not due to a contagium generated within a diseased body and spread by contact. Some authorities agreed with Hippocrates that the disturbing cause, derived from marshes, entered man's body in contaminated drinking water, or perhaps from that used for bathing. Other observers, more numerous, blamed 'bad air', the marsh effluvium arising from still water or warm mud. A few had noticed that there were also intermittent fevers in certain hill tracts. They preferred to speak more generally of febrific airs or exhalations originating in hill streams as well as in low-lying marshes. They



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learnedly wrote of the wide dispersal of vegeto-animal miasmata.

Italian physicians and country folk alike so usually referred to bad air as the source of intermittent fevers that, some time in the Middle Ages, the two words *mala* and *aria*, written *mal'aria*, lost their separating apostrophe and were joined as one word *malaria*, which referred as a rule not to the disease but to the exciting cause. In those parts of Italy where *cattiva* was a more commonly used adjective than *mala*, the febrific vapour was called *cattivaria*, a term still occasionally heard around Naples. It seems of some significance that common folk never accepted the term *malaqua* which had been used by some physicians who attributed the intermittents to bad marsh water rather than to bad air.

The word *malaria* does not occur in the first medical dictionary, which was published in 1719 by John Quincy, nor is it in the English dictionary of Thomas Blount published in 1656, or that of Stephen Blancard, translated from the Dutch in 1684. Probably it was first penned in English when Horace Walpole in 1740, while travelling in Italy under the tutelage of Thomas Gray the poet, wrote home, according to the *Oxford English Dictionary*, telling of 'A horrid thing called the mal'aria, that comes to Rome every summer and kills one.' Here the reference was to the cause and not to the disease. Shelley in 1818 spoke of 'a malaria fever caught *in the Pontine Marshes*'. By this time the apostrophe was usually omitted. Byron, for instance, in 1821, wrote, 'I staid out too late for this malaria season.' Other similar references could be cited. But the word *malaria* is not found in Johnson's 1827 *Dictionary of the English Language*, first published in 1755.

Through the courtesy of the British Museum, I was able to consult a unique publication by Francesco Cancellieri, dated 1817. The author mentions a 'Discorso do F. Jacquier sopra la mal'aria, e le malattie, che cagione principalmente in varie spiaggie d'Italia, in tempo di estate', published in Rome in 1743. I have not been able to find Jacquier's pamphlet but it would appear that he was first to use the term *mal'aria* in a medical text. Contrary to often repeated

statements, the word *malaria* does not appear in Torti's famous *Therapeutice Specialis* Several individuals, including myself, have searched very carefully without finding it

Perhaps the first to use the word 'malaria' in an English language medical textbook was John Macculloch in 1829 His treatise was generously titled, *Malaria, an Essay on the Production and Propagation of this Poison, and on the Nature and Localities of the Places by which it is Produced with an Enumeration of the diseases caused by it, and of the Means of Preventing or Diminishing them, both at Home and in the Naval and Military Services* Macculloch employed the word in the sense of a 'chemical substance called malaria' In his 1830 essay, he wrote, 'That intermittents of whatever type, are the produce of Malaria, is a fact as universally established as any thing in medicine can well be, '

The New York Public Library possesses the following interesting letter written to Noah Webster in 1831 by Dr Ennalls Martin, a practitioner in Talbot County, Maryland

Easton M [Maryland] Jan 30th 1831

Noah Webster Esq

Dear Sir

In the year 1815 I did myself the honor of dedicating to you an essay on the Epidemics of 1813, and 14 because I obtained more information from reading your 'History of Epidemics and Pestilential diseases' than from any other source whatever The object of now addressing you is to obtain further information on the same subject, but more particularly on a term lately introduced which is set down as the same as Miasmata, tho it is clearly and decidedly different in its intentional meaning I have looked in your excellent Dictionary for the word *Malaria*, but such a word does not appear in its pages, nevertheless I am of an opinion that the word may very properly [illegible]

the earth which you have so clearly proved, it would be a most appropriate term and might be used to great advantage but when made to signify the same as Miasmata, in my opinion it is absurd in the extreme!

I have an intention of contending for the prize, which is advertised

by the Medical and Chirurgical Faculty of this State (Maryland) but shall not put pen to paper until I have your Ideas upon the word *Malaria*, which is made synonymous with Miasmata That you may have clear Ideas of the subject, I shall transcribe a copy from the American Journal of Medical Sciences, which may be found in page 545 of the 12 No for August 1830, lest you should not lay your hands on it with convenience

We have had more rainy weather since the 10th of last October than the oldest person in the country has known There has scarcely been an interval of three days of clear weather since that time Frequently the rain has fallen in torrents On the 14th of this month a violent snow storm set in with great fury, which lasted for three days, choking up our lanes in such a manner as to make them impassable, which has occasioned great distress both in town and country for fire wood The thermometer has been down to 6 degrees, and the rivers have been frozen so hard as to induce persons to cross them in slays, which has not been the case for many years before

This county has been healthy during the summer and autumn, and the winter continues to be so to this date Is it not probable that we shall have a sickly spring? *Will not your history of Epidemics* induce us to look out for such an event?

Tho' the roads are very bad, I shall hope to hear from you in ten or fifteen days, and will subscribe myself

Your friend and admirer
Ennalls Martin M D

Prize Essay The Medical and Chirurgical Faculty of Maryland offers a premium of one hundred dollars for 'an Essay upon the nature and sources of Malaria or noxious Miasma from which originate the family of diseases usually known by the denomination of Bilious diseases, together with the best means of preventing the formation of Malaria, removing the sources and obviating their effects upon the human constitution, when the cause cannot be removed'

In the next edition after this letter, 1841, the *American Dictionary of the English Language* included the following definitions

Malaria, N /*mal* and *aria*, bad air, Ital /Bad air, that species of air which produces or tends to produce disease
Malarious, a Infected by malaria, unhealthy

These definitions were continued in the American Dictionary through the edition of 1900 The next one, that of

1910, called the *International Dictionary*, defined the word as follows

> Malaria N/It, contr fr *mala aria* bad air See Malice, Air/1 Air infected with a noxious substance capable of engendering disease esp an unhealthy exhalation from certain soils as marsh miasma
>
> 2 Med A febrile disease formerly supposed to be due to poisonous exhalations from the soil but now known to be due to the presence in the red blood corpuscles of animal parasites of the genus *Plasmodium*

So the early definition of the word *malaria* in English was not what it is today but was much closer to the original Italian Gradually, the word began to connote, beyond its derived meaning, a toxic substance and then a particulate pathogen, not always but often air-borne For instance, Oliver Wendell Holmes in his lecture on Homoeopathy and its Kindred Delusions, delivered in 1842 and first published in 1861, spoke of 'the poisonous influence of an atmosphere impregnated with invisible *malaria*'

The obvious term *malarial fever* became common and as early as 1860 Austin Flint Sr, in his popular *Treatise on the Principles and Practice of Medicine* wrote of 'periodical fevers, commonly known as malaria' But Sternberg in his textbook in 1884 emphasized the customary usage by stating that the word *malaria* 'should be limited in use to a special kind of poison' which produces the periodic fevers—'an unknown poison of telluric origin' Osler, however, in 1887 sometimes used the word *malaria* for the disease and not the aetiological agent, although in the first edition of his *Principles and Practice of Medicine* (1892) he preferred the term *malarial fever*

Billings, in his *National Medical Dictionary*, in 1890, defined 'malaria' as '1 The specific paludal miasm which is supposed to be the cause of ague and allied diseases 2 (F) Foul air' He defined 'malarial fever' as 'an endemic disease of wide geographical distribution, characterized by fever which usually has distinct periods of remission '

Thayer, in 1897, followed the usual practice and suggested that the word be used only as a qualifying adjective,

as in the expression *malarial fever* So too Manson, in the first edition of his classic text on *Tropical Diseases*, preferred 'malarial fever' rather than simply *malaria* But, since 1900, original meanings and connotations have disappeared and the word *malaria* now clearly refers to a specific group of intermittent febrile diseases caused by parasites of the genus *Plasmodium*

The word *malaria* was sometimes applied in a much wider sense as a 'disease-producing bad air' For instance, H Barker's Fothergillian Prize Essay of 1859 was entitled, *On Malaria and Miasmata and their influence in the Production of Typhus and Typhoid Fevers, Cholera and the Exanthemata* Henry Holland in 1840 had written of a 'migrating malaria—a wandering cause of disease—capable, not merely of being diffused through the atmosphere but also possessing the power of reproducing itself '

Another early name for the periodical fevers was *ague*, a word, incidentally, that displeased Voltaire when he was learning the English language while exiled in 1726 Why should 'ague' have two syllables but 'plague' only one? According to Durant, Voltaire exclaimed that for all he cared plague might take one half the English dictionary, ague the other

That the word *ague* might clearly refer to malarial fevers is witnessed by many authors For example, Sydenham in 1666, discussing the intermittent fevers of 1661–4, wrote that 'All agues begin with shiverings and rigor, succeeded by heat and terminated by sweats'

The first medical dictionary, that of Quincy in 1719, already mentioned, defined 'Agues' as follows

Intermitting Fevers of all kinds are of this class, and whether there is a cold fit or not, is of no great moment as to the Intentions of the Cure that being more accidental than essential hereunto, altho' indeed the Term Ague, if from *Algor*, Coldness as some will have it, is applicable only where the cold fit is sensible

However, *ague* is not derived from *algor* but from the Old French of the Latin *acuta*, sharp

William Grant in his text on *Fevers most Common in London*, printed in 1771, wrote that 'a true ague is to be

distinguished from every other fever by two symptoms, first, the *frigus, rigor*, and *horror febrilis* at the beginning of every fit, and secondly, an absolute apyrexia between the fits' William Buchan in his *Domestic Medicine*, 9th edition, published in 1781, wrote 'Of Intermitting Fevers or Agues' and he referred to these intermitting fevers as 'quotidian, tertian, quartan, etc ' He further said 'Agues are occasioned by effluvia from putrid stagnating water This is evident from their abounding in rainy seasons, and being most frequent in countries where the soil is marshy, as in Holland, the Fens of Cambridgeshire, the Hundreds of Essex, etc '

James Lind, in the 4th edition of *Essay on Diseases Incidental to Europeans in Hot Climates* (1788) added an appendix, 'On the Intermitting Fevers' In this he states that 'an intermitting fever, or what is usually termed an ague, is a disease peculiarly frequent in low, woody, and marshy places' He noted its 'similarity in England to the endemic of hot climates' and remarked that, 'In the proper administration of the bark, the cure of agues may be said entirely to consist '

Copland's *Medical Dictionary*, 1846, under 'Ague', refers the reader to 'Fever-Intermittent Fevers' Austin Flint, in 1866, defines 'intermittent fever' as 'fever and ague', 'chill fever', and 'the shakes'

But, as Sir William MacArthur points out, the word *ague* is older in literature than the word *malaria* and originally referred to any acute fever There is a passage by Chaucer (1340?–1400) in *The Nonne Prest His Tale*, which reads

> And if it do, I dar wel leye a grote
> That ye schul have a fevere terciane,
> Or an agu, that may be youre bane

Later, *ague* was a name often applied to typhus MacArthur notes that Shakespeare usually employed the word to mean malaria but once referred to spotted ague, which was typhus One must, of course, always be cautious about assuming that medical words like *ague* and *intermittents*, encountered in old treatises, meant to early authors what they now mean to us

Animalia Quaedam Minuta

Thomas Fuller, in 1730, was so impressed by the mystery of malaria that he exclaimed, 'Can any man, can all the men in the world, tho' assisted by Anatomy, Chemistry, and the best Glasses, pretend positively and certainly to tell us, what particles, how sized, figured, situated, mixed, moved, and how many of them are requisite to produce a quartan ague, and how they specifically differ from those of a tertian ?' Bartlett, over a century later in 1847, wrote,

> The essential, efficient, producing cause of periodical fever,—the poison, whose action upon the system gives rise to the disease —is a substance, or agent, which has received the names of *malaria* and *marsh miasm* The nature and composition of this poison are wholly unknown to us Neither the strongest lenses of the microscope, nor the nicest analyses of chemistry have succeeded in discovering the faintest traces even of the composition and character of these invisible, mysterious, and stupendous agencies

Impalpable magic, unseen demons, storm and thunder spirits, darts of malicious elves, miasma or contagion—what could the pathogen be? Some said there was no need to postulate either a miasma or a contagion The cause, more likely, was some such factor as change in temperature or certain types of food, or, as Doctor Buchan suggested in 1781, 'whatever relaxes the solids, diminishes the perspiration, or obstructs the circulation' Buchan listed 'eating too much stone fruit', 'a watery diet', 'damp houses', 'evening dews', 'fatigue and depressing passions, and the like' But there were some obvious snags in a theory of pure inflammation As Johnson wrote, 'What kind of inflammation must that be which explodes, as it were, the moment the clock strikes a particular hour, and this for days and weeks together?'

Greek philosophers had started the suggestion that matter is made up of small particles Anaxagoras (born about 500 B C) said that each kind of body is divisible into homogeneous parts or 'seeds', each of which retains the properties of the whole and is again divisible and so on to infinity This idea of 'seeds' was developed by the Stoics, by

Epicuros, and by others, and spread over into speculations as to the origin of disease Lucretius and his 'atoms or seeds' of disease has been mentioned above, and from his time onwards there were similar references, growing in volume and authority For instance, the scholar Thierry of Chartres, in the twelfth century, using the ideas of Anaxagoras and the Stoics, wrote that in the first stage of creation plants, animals and men were all made simultaneously in germs or in their 'seminal causes' Fracastorius in 1546 wrote of the *seminaria* of disease and went a good step ahead by suggesting that these seeds of disease might [illegible]

bodies Christian Lange (1619–62) wrote brilliantly about pathogenic *animata* Leeuwenhoek in 1676 actually saw and described micro organisms, but not in particular reference to disease

The germ theory of disease was brought still nearer by Harvey s belief that 'the egg is the common beginning of all animals', by Francesco Redi's experiments in 1668 which disproved spontaneous generation in insects, and by many another scholar's observations

However, despite Redi's demonstration, the theory of spontaneous generation died slowly Many still saw in miasmata arising from swamps some confirmation of such views as those held by the famous alchemist, van Helmont (1577–1644) He had said that 'the smells which rise from the bottom of morasses produce frogs, slugs, leeches, grasses, and other things This view was not much different from that of Aristotle, who had said, 'All dry bodies which become damp and all damp bodies which are dried engender animal life' Van Helmont in one fascinating passage, wrote,

It suffices to press a dirty shirt into the orifice of a vessel containing a little corn After about twenty one days the ferment proceeding from the dirty shirt modified by the odour of the corn effects the transformation of the corn into mice The mice are born full

grown. . . . There are both males and females. To reproduce the species it suffices to pair them.

But during the eighteenth and early nineteenth centuries the germ theory continued to evolve and belief in the specificity of contagious diseases was growing, as evidenced by the writings of such men as Thomas Fuller (1657–1734). He said that one disease could not change into another 'any more than a Hen can breed a Duck'. Bretonneau (1778–1862) added his prestige to the hypothesis of microscopic pathogens and he has been called by some the founder of the doctrine of the specificity of diseases, an idea that he expounded vigorously. So, too, Schwann (1810–82) by his cellular theory had a great influence in accelerating the development of the germ theory. Finally, came the clear demonstrations by Bassi (silk-worm disease), Henle, Pasteur (who, to use his own expression, showed 'where the mice got in'), Koch, and Lister.

Quite naturally, therefore, the idea of a living and multiplying microscopic organism as the cause of the intermittent fevers gained ground and invited experimentation.

Of course, there were those who, like North as late as 1896, referred sceptically to the idea that minute organisms, the *animalia quaedam minuta* of Cato, Varro, and Columella, Pasteur or Koch, could enter man's body and give rise to intermittent fevers. Borrowing an Italian term, North, with some spirit characterized the germ theory of the causation of malaria as the *pregiudizio palustra.* He found more satisfactory the theory that malaria was caused by the action upon the human body of those peculiar climatic conditions that had been shown to prevail in certain malarious places. North cited Oldham's 1871 chill theory that malarial fevers are due to the action upon the human organism of the violent climatic changes which are found 'in all malarious countries'. Indeed, said Oldham, 'Malaria is chill.'

Others blamed sulphuretted hydrogen, ammonia, and related chemical compounds. Some observers, like Boudin in 1841, assigned the cause of malaria to extracts of certain plants, such as *Chara*.

Agostino Bassi, mentioned above, stated that a physician

of Milan, Giovanni Rasori, who died in 1837, had written to him expressing agreement in his discovery of the pathogenic organisms of silkworm disease and outlining very clearly some personal beliefs about malaria, as follows 'For many years I have held that the intermittent fevers are produced by parasites which renew the paroxysm by the act of their reproduction, which occurs sooner or later, according to the variety of their species In this way the intermittent fevers, quotidian, tertian, and quartan, arise' Rasori had scored a bull's eye on the target, but neither he nor any contemporary knew it Most observers agreed with Bartlett that there was no reason 'to believe or to hope that the thick darkness which has ever wrapped and still wraps this intermittent physiological phenomenon, so full of mystery and wonder, will ever be dispelled'

Bartlett had summarized the theories of the causation of periodical fever under four headings (1) all possible chemical products and compounds in wet marshy localities, (2) moisture alone, (3) products of animal and vegetable decomposition, (4) invisible, living animalculae He considered the fourth 'surmise' to be the 'best hypothesis'

J K Mitchell in 1848 published an essay on the *Cryptogamous Origin of Malarious and Epidemic Fevers* Mitchell wrote as follows

> The only theoretic view of malaria to which I incline, is that which refers marsh fevers, and some of the epidemic diseases to a living organic cause, capable of reproduction by germs, as is alleged of contagious diseases, but unlike the latter in this, that the germs are not reproduced by the organism of the sick but exteriorly to, and independently of, the human body In other words that, as the germs of contagious diseases are reproduced in the body, the germs productive of malarious and other non contagious diseases are elaborated and re elaborated out of the body, and independently of its agency One is a product of person, the other of place

Mitchell believed the cause of malaria was a fungus He hoped that someone would investigate his ideas

Daniel Drake (1785–1852) was another observer who was much interested in the origin of malaria He, too, did not believe meteoric or malarial hypotheses but was convinced

that the aetiologic agents were 'living organic forms, too small to be seen with the naked eye, and which may belong either to the vegetable or animal kingdom, or partake of the characters of both' He visualized a 'countless variety of organic forms in the aerial ocean in greater multitudes than elsewhere ' Drake noted that among visible plants and animals some were harmless to man but some, like the rattlesnake, bee, and gnat could inflict damage So, he said, 'It seems justifiable to ascribe, by analogy, to microscopic animals and plants, the same diversity of properties which we find in larger beings, differing from them, as we may presume, in nothing but size and complexity of organization We may suppose, then, that while many species of this minute creation are harmless, there are others which can exert upon our systems a pernicious influence ' Drake commented further, 'Now, may it not be, that two distinct species of the same natural order of microscopic beings, may produce autumnal fever? May not one be the cause of intermittents—the other of remittents? May not both act on the system at the same time? And may we not thus explain diversities, which are inexplicable on the malarial hypothesis?' He concluded, 'Ignorant, however, as we are of any definite, efficient cause for autumnal fevers I am a full believer in its existence, and shall speak of it as a specific agent, known only by its effects on the living body if I should at any time use the word malaria, it is merely to designate the remote cause, *whatever* it may be '

One of the earliest attempts to incriminate a microscopic organism as the cause of malarial fevers was made by Salisbury in the United States in 1862–6 He found in the sputa of malaria cases 'a great variety of zoospheroid cells, animalcular bodies, diatoms, algoid cells and filaments and fungoid spores' But the only constant findings were minute oblong cells with distinct nuclei and cell walls These spores he called *Gemiasma*, and it seemed to him that they were only found in cases of malarial fever or in malarious localities So he concluded that they were 'the only true source of intermittent and remittent fever He explained that these spores became elevated and suspended

in the heavy, humid night exhalations of ague districts and that they were poisonous to the epithelial surfaces of the body He placed boxes of earth containing such spores in the bedrooms of volunteers and, because the experiments were being carried out in a malarious place, it so happened that most of his subjects developed fever

Binz, experimenting with quinine in 1868, surmised that 'malaria was caused by some low form of animal life, and the curative action of quinine is due to its direct effect upon this micro-organism' Here was another astute conjecture

In 1869 Pietro Balestra, in Ostia and Maccarese at the mouth of the Tiber, cultured a microphyte which he called *Alga miasmatica* The spores were widely distributed in the marsh air and marsh dew and seemed to be proportional in numbers to the malariousness of the area Doctor Balestra himself voluntarily inhaled the air of a large culture dish in which this alga was growing and soon thereafter he had fever Other investigators found other spores which also seemed to cause fever when inhaled Massy, in Ceylon, believed that he had incriminated a microscopic fungus as the aetiologic agent, Van den Corput in Europe found a suspicious algal grown, and there were many similar discoveries

In 1879 Professor Klebs and Tommasi-Crudeli, scientists of repute in Italy, published careful studies on the causation of malaria They had isolated a rod-like organism which they named *Bacillus malariae* They recovered this bacterium from air and mud of malarious marshes and also from the urine of a patient and they grew it on various culture media They injected it into rabbits and believed that they induced intermittent fever in these animals (now known to be insusceptible to malaria) with enlargement and pigmentation of the spleen

As Scott points out, this period in the history of malariology illustrated Pasteur's dictum 'Be very careful when you are looking for a thing or you will be sure to find it'

2

THE PARASITE

Eyes on the Pigment

By 1875 the presence of granules of dark grey-black 'paludic pigment' in the tissues and blood of malaria patients had become known. At first the pigment was not directly attributed to intermittent fevers. Lancisi in 1716 and Bright in 1831 had described it in spleen and brain sections taken post-mortem. Several others also reported it. For example, Heinrich Meckel in 1847, in preparations of blood, brain, and spleen, noticed certain round, ovoid, or spindle-shaped protoplasmic masses containing black irregular pigment granules. He wrote of isolated 'pigment cells containing a visible nucleus' as bodies distinct from blood-cells. His clear description suggests that unsuspectingly he was looking at malaria parasites. But his patient had a psychiatric disease and Meckel in his report does not mention intermittent fever, although the autopsy findings strongly suggest chronic malaria.

Perhaps the first who definitely tied to malarial fevers the pigment that we now call haemozoin were Virchow and Frerichs, in 1848. The drawings of Frerichs, published in 1858, so clearly suggest plasmodia that I believe he, too, must have been looking at plasmodia, without realizing their significance.

Julius Planer, in 1854, described the pigment in the blood, and there was an increasing number of references in the literature. Delafield wrote in 1872 that in malaria 'the most constant lesion is the presence of little particles of black or reddish pigment in the blood. The pigment is in the form of flakes or of granules embedded in small, irregular, transparent, finely granular bodies. We also find the same transparent bodies without pigment.' Here again were the parasites, seen but unrecognized as such. Kelsh

in 1875 also saw these granules in the blood corpuscles of malaria patients and concluded, in 1880, that they were a diagnostic character

Another interesting report was that of Professor Joseph Jones of the University of Louisiana In 1876 he stated that he could clearly distinguish the changes induced in blood by malaria In fact, he was able in a medico-legal case to testify that certain stains on the coat and shirt of an accused prisoner were not paint, as had been affirmed, but were blood and moreover were the blood 'of a human being who had suffered and was probably suffering at the moment when the blood was abstracted, with malarial or paroxsymal fever' Jones described the characteristic pigment and stated that 'many of the particles of the melanemic pigment were spherical, others irregular and angular, some entirely free, others encased in a hyaline mass ' He, like Meckel and Delafield, was actually, but unknowingly, describing malaria parasites It should not be forgotten that these observers did not have the benefit of modern dyes in their blood-smear microscopy

The Malaria Parasite Recognized

Naturally, the malaria pigment had aroused curiosity in many observers It was commonly attributed to the deterioration in the blood itself brought about by the marsh miasma One who became particularly keen to know more about the pigment was Charles Louis Alphonse Laveran, a French Army surgeon stationed in North Africa Beginning in 1878, at the Military Hospital in Constantine, Algeria, he spent much of his time looking at post-mortem tissue and particularly at preparations of fresh blood taken from malaria patients in Bone, Biskra, and Constantine His strongest microscope lens gave him a magnification less than half as great as we now consider desirable for observing malaria parasites Furthermore, he did not have the differential stains, developed a decade later, which, by colouring specific parts of blood cell or parasite characteristic shades of blue or red, have greatly facilitated the examination of blood smears But Laveran did have

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perseverance and intelligence. Most important was the fact that Laveran was ready for the great moment when it came. For, as Pasteur at his inaugural lecture at Lille in 1854 told his students, 'in the field of observation, chance only favours the mind which is prepared'.

Laveran found the pigmented bodies previously described by others. But he looked at them with more than mere confirmation in mind and he discovered their true significance. Quoting from his report, Laveran said, 'I had suspected for a long time the parasitic nature of these bodies when on November 6th, 1880, while examining one of the spherical pigmented elements in a preparation of fresh blood, I noticed with joy at the periphery motile filaments of the animated nature of which there was no room for doubt.' Here was a living parasite seen at last with recognition of its significance, and thus did Laveran enter into that small company of the Immortals of Medicine. He received a Nobel Prize in 1907 for his achievement.

Laveran named his new-found organism, *Oscillaria malariae* and stated that it was entirely distinct from the *Bacillus malariae* of Klebs and Tommasi-Crudeli. He described amoeboid, rosette, and crescent, as well as the flagellating forms, but he did not succeed immediately in fitting them together in their proper life-cycle relationships. However, his basic discovery was soon confirmed by a colleague, Dr. E. Richard. But both announcements were received with scepticism because of the very long list of so-called malaria parasites of all sorts which had been found and proclaimed with equal certainty by others.

In 1881 Laveran took some of his microscope slides to Rome and showed them to Ettore Marchiafava, Angelo Celli, Baccelli, Giuseppe Bastianelli, and Camillo Golgi. These observers had oil immersion lenses of greater power than Laveran's dry lens and they had plenty of malaria patients available for study. Marchiafava and Celli especially had been very doubtful about Laveran's findings, but after meeting him and seeing his slides, they became enthusiastic supporters and were able rather rapidly, in

Fig. 1. Globule rouge du sang. — Fig. 2 Leucocyte granuleux. (Ces éléments sont destinés à servir de point de comparaison pour apprécier les dimensions des autres éléments dessinés au même grossissement de 1000 diamètres environ.) — Fig. 3 et 4. Corps n° 1. — Fig. 5. Corps ovalaire intermédiaire aux corps n° 1 et n° 2. — Fig 6. Corps n° 2 immobile. — Fig. 7. Corps n° 2 avec ses filaments périphériques mobiles, renflés à leur extrémité libre. — Fig 8 Corps n° 2 avec appendices mobiles groupés latéralement. — Fig. 9 Filament mobile devenu libre. — Fig. 10. Corps sphérique rempli de granulations pigmentaires mobiles — Fig. 11. Corps n° 3. — Fig. 12 et 13. Corps n° 3 déformés. — Fig. 14. Éléments pigmentés provenant du sang d'un homme mort de fièvre pernicieuse : a, a' éléments analogues aux corps n° 1 ; b, b', b" éléments analogues aux corps n° 3 — Fig. 15 Éléments dissociés de la rate d'un homme mort de fièvre pernicieuse ; éléments analogues aux corps n° 3.

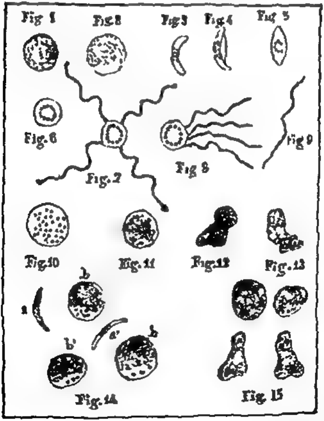
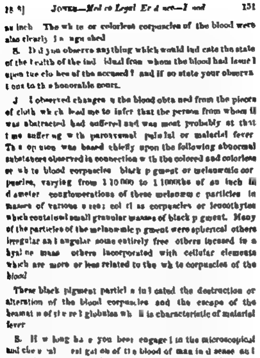


FIG 4 Plasmodia as drawn by Laveran in his original communication to the Societé medicale des Hopitaux, 24 Dec 1880

Courtesy of the Pasteur Institute of Paris and Med Gen Vaucel



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an inch. The white or colorless corpuscles of the blood were also clearly distinguished.

5. Did you observe anything which would indicate the state of the health of the individual from whom the blood had issued upon the clothes of the accused? and if so state your observations to this honorable court.

A. I observed changes in the blood obtained from the pieces of cloth which lead me to infer that the person from whom it was abstracted had suffered and was most probably at that time suffering with paroxysmal, paludal or malarial fever. This opinion was based chiefly upon the following abnormal substances observed in connection with the colored and colorless or white blood corpuscles: black pigment or melanaemic corpuscles, varying from 1 10,000 to 1 1000ths of an inch in diameter; conglomerations of these melanaemic particles in masses of various sizes; colorless corpuscles or leucocythes which contained small granular masses of black pigment. Many of the particles of the melanaemic pigment were spherical, others irregular and angular, some entirely free, others incased in a hyaline mass, others incorporated with cellular elements which are more or less related to the white corpuscles of the blood.

These black pigment particles indicated the destruction or alteration of the blood corpuscles and the escape of the haematin of the red globules which is characteristic of malarial fever.

8. How long have you been engaged in the microscopical and chemical investigation of the blood of man in disease, and upon what facts do you base the preceding statement?

A. My investigations upon the chemical and microscopical changes of the blood in fevers, and especially in malarial and yellow fevers were commenced in 18.. and have been continued to the present moment, and during the past ten years I have treated in the wards of the Charity Hospital of New Orleans over four thousand cases of various diseases, more than one-half of which were due to the action of the malaria of the swamps and marshes of the Mississippi valley.

FIG 5 Photograph of a page from a publication of Professor J Jones in *New Orleans Medical and Surgical Journal*, 1878–9 Jones in a medico legal case infers that certain blood stains came from a person suffering from malaria because in the blood he saw, microscopically, some abnormal substances his experience had taught him to associate with this disease There is little doubt that he had often seen malaria parasites unrecognized as such

Courtesy of the Armed Forces Medical Library Washington

DE

NOXIIS PALUDUM

E F F L U V I I S,

Eorumque Remediis.

L I B R I D V O.

Auctore

J O: M A R I A L A N C I S I O

Ab intimo Cubiculo, & Archiatro

S A N C T I S S I M I P A T R I S

C L E M E N T I S XI.

P O N T. M A X.

ROMÆ Anno MDCCXVII. Typis Jo. MARIÆ SALVIONI

In Archigymnasio SAPIENTIÆ.

SVPERIORVM FACVLTATE.

FIG. 6 Title page of Lancisi's *De Noxiis Paludum*

Courtesy of the Ross Institute

1882–4, to set up the status of the new parasite on a firm basis They not only saw the various forms described by Laveran, but they found the young unpigmented stages in the corpuscles, they demonstrated that the characteristic melanin was found within the parasite and they noted that multiplication was by fission Marchiafava and Celli stated unequivocably that 'The malaria infection is produced by a parasite *sui generis* which invades the red corpuscles, lives within them, and is developed at the expense of their substance, converting their haemoglobin into melanin, and which multiplies by fission '

Then Golgi in Pavia in 1885–6 demonstrated the relation between the cyclical development of the parasites and the long-known and characteristic periodical succession of febrile paroxysms, also the constant relationship of individual attacks to the development, maturation, and reproduction of a generation of parasites He was first to describe the quartan parasite and to differentiate it from that of tertian fever, and he noted the absence of crescents in these two infections Golgi was awarded a Nobel Prize in 1906, not for his malaria observations but for his outstanding studies on the structure of the central nervous system

Of course, not all observers accepted the new reports Many agreed with Professor Tommasi-Crudeli who wrote in 1886 that

> the changes described in the blood corpuscles were not due to the development in them of an animal parasite (which thus far no one has been able to discover, either in the air or in malarious localities) but that on the contrary, it is the effect of the degeneration of the red corpuscles due to the direct or indirect operation of a disease producing ferment of an entirely different nature

There was a stumbling-block in the shape of Henle's principles, which had become the famous postulates of his pupil Koch after the latter had tested them in regard to anthrax These conditions stipulated that suspected pathogens must be isolated and then proved to be capable of producing the characteristic disease in another individual

No one had succeeded in isolating the new organism of Laveran as a living culture in a test-tube.

Among the most notable sceptics was William Osler, at the time well on the way towards that outstanding pre-eminence that was universally his for so many years. Osler attended the inaugural meeting of the Association of American Physicians in Washington, 17–18 June 1886. One of the papers presented was by young W. T. Councilman, from Welch's laboratory in Johns Hopkins, and he discussed 'Certain elements found in the blood of malarial fever'. Councilman believed that he had seen Laveran's bodies but he was not certain that they were the cause of malaria. Among those who listened to the presentation probably no one had had more experience in the microscopic study of blood than Osler. So doubtless he had most of the audience in agreement with him when he expressed strong doubt as to the nature of the so-called malaria bodies. Osler said he had examined six patients, in three of whom he had seen these amoeboid objects, but in his opinion they were only vacuoles in the red cells. Sternberg, who had confirmed Laveran's discovery, at least to his own satisfaction, arose and suggested that if Osler would stain his blood smears he would have no doubt that he was looking at Laveran's parasites. But almost no one agreed with Sternberg.

Nevertheless, Osler's confidence in his own view was shaken. Since he was not a man to leave matters thus unsettled, he went back to Blockley Hospital in Philadelphia, where he was Visiting Physician, and immediately set to work to settle the issue. Thus started a special interest in malaria that he never gave up. Osler postponed his Canadian vacation, despite intense heat, and he examined blood smears from every case of malaria that he could find, without much success at first. Indeed, in September he editorialized on the subject for *Medical News*, stating that he was still hesitant about accepting the new parasite. Virchow had just reported finding a micrococcus in the blood of malaria patients and others were insistently claiming this or that 'malaria germ', but as Osler commented in his editorial, all 'cultures have failed'. He added, 'In view

of the lamentable mistakes which have been made in this disease by so many good observers, the most rigid scrutiny should be exercised in accepting evidence ' However, by the end of the month Osler had found crescentic forms about which he had no doubts and he soon became completely convinced of the validity of Laveran's parasites On 28 October 1886 he reported this to the Pathological Society and in 1887 he published his famous studies on *The Haematozoa of Malaria*

Osler was very frank about his conversion He said, 'When I first read Laveran's papers nothing excited my incredulity more than his description of the ciliated bodies It seemed so improbable and so contrary to all past experience, that flagellate organisms should occur in the blood ' Osler acknowledged that, 'The work of the past six months has taught me a lesson on the folly of scepticism based on theoretical conceptions, and of pre-conceived notions drawn from a limited experience ' Thereafter, Osler always insisted that the diagnosis of malaria be based on an examination of blood smears It was largely due to Osler's subsequent writing and teaching of this and other principles of malaria diagnosis and treatment that the confusing hybrid disease, typho malaria, was driven out of textbooks and medical meetings, after a long battle

In 1885–7 Danilewski, a Russian physiologist who was at the time unaware of Laveran's studies, discovered malaria parasites in birds Then in 1889–90, Pietro Canalis and also Celli and Marchiafava demonstrated and clearly differentiated a third species of human malaria parasite, the one now called *Plasmodium falciparum*, which has the crescentic stages not found in the species *vivax* and *malariae* Welch named the aestivo-autumnal parasites *falciparum*, deriving the name from *falx*, sickle, and *parere*, to bring forth Osler in 1887 really anticipated this finding but did not formulate the sharp differentiation of *Plasmodium* into three species Then in 1890–1 in old St Petersburg, D L Romanowsky devised a new differential blood stain which made it much easier to recognize the parasites and their nuclei and chromatin, thus greatly facilitating subsequent studies

Sakharoff in 1894 demonstrated the chromatin in plasmodia (including the flagella)

Stephens in 1922 described the fourth species of plasmodia infecting man He found it in smears from West Africa and he named it *Plasmodium ovale*

One further historical item of interest may perhaps be inserted parenthetically at this point It is the discovery long before plasmodia were known, that the distribution and incidence of malaria in a community could be surveyed by systematically palpating the enlarged spleens From the time of Hippocrates, splenomegaly had been associated with the intermittents but it was Dempster in India in 1847 who first made practical use of spleen surveys to measure malaria in communities As Hirsch wrote in 1886, splenic enlargement 'is not only coincident exactly with the distribution of malarial fevers, but everywhere it keeps pace with the latter closely in their extent and severity of type'

3

THE MOSQUITO

Mode of Infection

By 1895 the validity of Laveran's malaria parasite was widely accepted by observers but no one knew in what manner man usually became infected Gerhardt, in 1884, had proved that healthy persons could be inoculated with malaria by injections of blood from malarious patients But how did natural infections occur? As already described, theories were plentiful enough but proof was lacking

Who first suggested that mosquitoes transmit malaria we do not know But there is excellent authority for believing that over the centuries some laymen close to nature and a few professional observers had come to suspect mosquitoes as instruments in the dissemination of fevers, especially the intermittents There is for example the following early Sanskrit reference published by Sir Henry A Blake, while he was Governor of Ceylon He had found it in Susruta, a work probably no more recent than the sixth century B C and possibly much older

ANCIENT THEORIES OF CAUSATION OF FEVER BY MOSQUITOES [1]

By His Excellency Sir Henry A Blake G C M G, &c
Governor of Ceylon

In the course of inquiries into the causation of an epidemic of malarial fever in Mutwal a division of the town of Colombo, l year I received a report from fifteen members of the Sinhal Medical Association in which it was mentioned incidentally according to ancient authorities on Ayurvedic medicine the causes of the disease are impure air and water and the existence mosquitoes I requested more precise information showing

[1] A paper read before the Ceylon Branch of the B M Association on 15th April 1905

mosquitoes were associated with the causation of malarial fever, and in reply I received extracts from ancient Indian works, among them an extract from Susruta, a Sanskrit work compiled, I am informed, from one of the lost Vedas The age of the work is not known, but as it was referred to in the works of a contemporary of Kalidása, the great Sanskrit poet who flourished in the sixth century of the Christian era, the work is at least 1,400 years old

The following are the passages They are taken from the Sanskrit edition published in 1873, and will be found at pages 43 and 45 (Kalpasthanam) —

तुङ्गीनासो विचिलकस्तालको वाहकस्तथा ।
कोष्ठागारी क्रिमिकरो यश्च मण्डलपुच्छकः ॥
तुङ्गनाभः सर्षपिकोऽवल्गुली शम्बुकस्तथा ।
अग्निकीटश्च घोराः स्युर्द्वादश प्राणनाशनाः ॥
तैर्भवन्तीह दष्टाना वेगज्ञानानि सर्पवत्
तास्ताश्च वेदनास्तीव्रा रोगा वै सान्निपातिकाः ॥
क्षाराग्निदग्धवद्दंशो रक्तपीतसितारुणः ।
ज्वराङ्गमर्दरोमाञ्चवेदनाभिः समन्वितः ॥
छर्द्यतीसारतृष्णा च दाहो मोहविजृम्भिका ॥
वेपथुश्वासहिक्काश्च दाहः शीतञ्च दारुणम् ॥
पिडकोपचयः शोफो ग्रन्थयो मण्डलानि च ।

Translation

KITA

Life-destroying terrific twelve kinds —

Tungináša	Mandalapuchchhaka
Vichilaka	Tunganàbha
Tálaka	Sarshapika
Wáhaka	Avalguli
Koshtágára	Śambuka
Krimikara	Agnikíta

Their bite is as painful as that of serpents, and causes diseases resulting *from the three humours joined together*, the *bite*, as if burnt with caustic or fire, is red, yellow, white and pink colour,

accompanied by fever, pain of limbs, hair standing on end, pain, vomiting, diarrhœa, thirst, heat, giddiness, yawning, shivering, hiccup, burning sensation, intense cold, vesicles or pustules increasing, swelling, knots under the skin, circles, &c

मशकाः सामुद्रः परिमण्डलो हस्तिमशकः कृष्णः पार्वतीय इति पञ्च। तैर्दष्टस्य तीव्रकण्डूर्दंशशोफश्च। पार्वतीयस्तु कीटैः प्राणहरैस्तुल्यलक्षणः॥

Translation

Masakáh (Mosquitoes) are of five kinds —

Sámudra	Krishna
Parimandala	Párwatiya
Hastimasaka	

Their bite causes swelling on the part bitten, itching As for the parwatiya, it has similar qualities to life-taking insects

H SUMANGALA High Priest,
Principal Vidyódaya College, Maligakanda

M ÑANISSARA,
Assistant to the Principal, Vidyódaya College

I SARVESWARASARMA, Brahmin

SIMON DE SILVA, Gate Mudaliyar,
Chief Sinhalese Translator to Government

R C KAILASAPILLAI, Mudaliyar,
Chief Tamil Translator to Government

March 3, 1905

That the translation should be verified satisfactorily I invited five Sanskrit scholars of acknowledged authority to meet at Queen's House The translation is that unanimously adopted by these five gentlemen, who have signed the extract

These passages, written possibly three thousand, and at least fourteen hundred years ago, are of singular interest, foreshadowing as they do the great discoveries of Manson and Ross

Truly there is no new thing under the sun

Here, to be sure, is a *pot-pourri* but, as Garrison has noted, it does contain a recognizable description of malaria and the suggestion that mosquitoes might carry diseases, possibly including that which causes chills and fever.

Numerous observers have reported local beliefs in an

association between mosquitoes and fevers For instance, Nuttall stated that Professor Lustig of Florence communicated to him an old belief in the mosquital origin of malaria by Italian peasants, Professor Rubner told him that his idea also existed in southern Tyrol, and Ronald Ross wrote to him of a similar belief held in parts of Africa and Assam Professor Koch related to Nuttall that negroes of the Usambara Mountains called malaria *Mbu* because they thought that the disease came from the *Mbu* or mosquitoes which stung them and gave them the disease when they went to the lowlands Richard Burton in his *First Footsteps in East Africa*, published in 1856, stated that in Somaliland certain tribesmen believed that mosquito bites caused deadly fevers The Abbé de Fortis, telling of his *Voyage in Dalmatia* in 1774, referred to his meeting with an ecclesiastic who thought fevers were due to insects conveying poisonous miasmata One realizes, of course, that travellers' tales have often been fanciful and one recalls that Herodotus gave currency to stories about fox-sized ants skilled in the mining of gold in north India (Book III, Chap 102–5) But some of these mosquito-malaria stories seem quite convincing

Giovanni Maria Lancisi, a Roman and the greatest Italian physician and epidemiologist of his time, in 1717, published a notable treatise on swamp fevers (*de Noxiis Paludum Effluviis eorumque Remediis*) in which he suggested that since malaria disappeared after drainage it must be due to some sort of marsh poison, possibly transmitted by mosquitoes As a naturalist, he studied these insects and concluded that they 'inoculated their own bad humours into our blood' Lancisi wrote,

Furthermore, no controversy can surely arise among professional men concerning the harmful effect which the insects of swamps inflict upon us by mixing their noxious juices with their saliva and gastro-intestinal fluids For, as I have shown above at length, their proboscis is always wet, and, as all their viscera are full of deleterious liquids, it is not possible that the juices rolling down with food and liquids into the stomach, are not there mixed with our ferments For this reason, we may conclude that marshy insects are highly

injurious to the body of man by the inmixture of deadly juices as well as by the withdrawal of the useful ones which are in us

Lancisi planned a drainage scheme for marshy regions, remarking, 'It is better not to fall ill than to be cured'

In 1790 Rush, of Philadelphia, informed his students that it seemed to him possible that fevers could be carried from marshes by insects He said, 'Some facts seem to prove this view' But it does not appear that Rush applied this idea to yellow fever, or very clearly to malaria

The animalcular hypothesis of disease came in for more attention as regards malaria when numerous observers pointed out the puzzling facts of marshes without malaria and malaria without marshes Bad air, swamp miasmata, seemed less and less certainly the keys to the mystery Perhaps the first in America to advance vigorously ideas of the animalcular origin of fevers was Doctor John Crawford, described by Welch as the 'best trained, most original, and experienced physician of his day in Baltimore' He had been born in Ireland, had been a surgeon in East India Company ships, and had also practised in Barbados and in the Colony of Demerara, finally settling in Baltimore and resident there from 1796 until his death in 1813

There has been much confusion as to Crawford's views about malaria For instance, it has been stated that he published an article in 1807 on *The Mosquital Origin of Malarial Disease* in the Baltimore *Observer* Nuttall said that Thayer and King told him they had searched carefully but could not find this article either published or among Crawford's papers nor could they find any reference by Crawford to malaria and mosquitoes I have recently made a similar search and am convinced that the paper mentioned above does not exist

However, there was published at weekly intervals from 20 November 1806 until 26 December 1807 in Baltimore, *The Observer and Repertory of Original and Selected Essays in Verse and Prose, on Topics of Polite Literature, etc* According to Ackerknecht, the editor was Crawford's daughter, but her name does not appear in the publication Through the courtesy of the Maryland Historical Society

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I asked myself whether the atmosphere by which I was surrounded and continually inhaling, could be less replete with these little beings?

Here Crawford was apparently describing dust particles as flies

So, while Crawford was a pioneer in America as regards the animalcular hypothesis, he does not appear to have suggested a specific transmission of malarial fevers by mosquitoes Unfortunately, Crawford's notes in the *Observer* caused him to be regarded as a crack-pot and markedly reduced his medical practice

Certainly, one must always consider contemporary connotations The word 'insect' for instance, seems clear enough today but in the early nineteenth century it was obviously not at all the same in its several meanings This is again made evident by quoting an anonymous reviewer of Macculloch's book on malaria in 1828 who wrote as follows

> The times and seasons, the places and circumstances, where miasma abounds, are the same as where insects abound Universally so Insects are of all sizes from the largest to the myriads of various kinds, which nothing but the most powerful microscopes can exhibit to our sight But large or small, the laws of their production are the same The circumstances that will produce a gnat, will produce an insect something less

Here, obviously, the word 'insects' meant about what the word 'bugs', used colloquially, means today So, too, Henry Holland, when in 1840 he wrote a chapter 'On the hypothesis of insect life as a cause of disease', used the word 'insect' to refer not only to bees, wasps, and ants, but also to 'minute or invisible insect species'

Ackerknecht has pointed out ... g animalculae
Clark Nott, born in South Carol ... 1848, Jo
Alabama, published the suggesti ... d in M
but insec ... the lowlands we ... arsh
yellow ... al fevers, he w ... ble ca
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Howev ... d Nott's pap ... mos
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t f

though the mosquito theory of their transmission had already been advanced He adds his belief that yellow fever, too, is mosquito-borne It is true that under 'insects' he undoubtedly includes animalculae as well as mosquitoes and he refers to 'the doctrine of insect or animalcular origin of disease' not as Holland's . . . So Nott's position is not [illegible] sages (possibly stem- [illegible]

It would appear that Malaria embarrasses its friends very much, not only by the irregularities of its journeyings over water, but by those over dry land The altitudinal range' of Malaria is a point of endless confusion A hill may suffer more than a valley It would certainly be quite as philosophical (as the Malarial theory) to suppose that some insect or animalcule, hatched in the lowlands, like the musquito, after passing through its metamorphoses takes flight, and either from preference for a different atmosphere or impelled by one of those extraordinary instincts which many are known to possess, wings its way to the hilltop to fulfill its appointed destiny

Nott also remarked that, 'The Itch is a contagious disease which may be transported from place to place in all seasons and all climates, and is unquestionably propagated by insects '

The truth of the matter seems to be that Nott's theory was somewhat broader than one of simple mosquito transmission It pointed to 'insects or animalcules' But it does appear to have included rather clearly the 'musquito'

Daniel Drake in his classic of 1850 noted that,

autumnal fever prevails very unequally in different years throughout the visible organic domain reproduction is by no means uniform It has often happened that mosquitoes have been absent, from the banks of the middle portion of the Ohio river, for a year, and in the next appeared in increased numbers We have but to suppose insect forms of a parallel size, to live under corresponding laws and the [vegeto animalcular] hypothesis offers an explanation of sickly and healthy seasons

Here Drake was near the truth but clearly was not thinking of mosquitoes as vectors He was postulating microscopic 'insects' as the pathogens of the intermittent fevers

Louis Daniel Beauperthuy was perhaps the first medical observer to make an unequivocal accusation against mosquitoes. Boyce, in *Mosquito or Man* quotes him as writing from Venezuela in 1854, as follows:

> The absence of mosquitoes during cold weather explains the dis- [illegible] and due to the prevalence of mosquitoes. . . . The mosquito inserts through the skin his suction apparatus (an instrument in the shape of a sharp hollow needle armed with two lateral saws) and injects into the wound a lethal fluid which may well be likened to the venom of a poisonous snake. . . .

Celli states that in 1870 Angelo Alessandrini in an agrarian and hygienic study on Rome and Latium wrote, 'the mosquito, with the vehicle of the unhealthy air from the open country, passes into inhabited places, invades the habitations, hides itself during the day to hum in the night in search of man in repose, . . . and, by means of its bite, inoculates its poison'.

The clearest statement of speculations about mosquitoes was read before the Philosophical Society of Washington in 1882, and published in 1883, by Albert Freeman Africanus King, an Englishman who went to America as a boy, became a doctor, and practised for nearly fifty years in Washington. King listed nineteen reasons why be believed that mosquitoes were the transmitters of malaria. In a footnote, he stated that most of his reasons 'were quoted from a paper read by Dr. John T. Metcalfe, United States Sanitary Commission'. Metcalfe's article was published in 1863 under the title, 'Nature and Treatment of Miasmatic Fevers' and listed some basic observations on the epidemiology of malaria, but made no mention of mosquitoes. King quoted most of Metcalfe's points and showed how well in each case his own mosquito theory would apply. For example, both malaria and mosquitoes are associated with marshes; both are encouraged by turning the soil; both are diminished by cultivation; both abound most after sundown; and both are arrested by mosquito nets. (Laveran's

parasite was not listed, for King appears to have been unaware of it) King concluded, 'While the data to be presented cannot be held to prove the theory, they may go so far as to initiate and encourage experiments and observations by which the truth or fallacy of the views held may be demonstrated, which, either way, will be a step in the line of progress'

I can find no record of any attempted observation stimulated by King's paper Perhaps the fact that King recommended that Washington be invested with a colossal woven-wire screen as high as the Washington Monument cast doubt on his sanity Yet malaria and its local vector offered a wealth of experimental material in Washington at that time, when Potomac Park was a festering marsh and the city fully deserved the satirical description of 'Swamppoodle' applied to it by the relentless Mrs Trollope

Manson's Role

Patrick Manson in 1894 gave the mosquito theory of malaria transmission its greatest impetus up to that time Born in Aberdeenshire in 1844, he had become a physician and had gone to the Orient to practise From 1866 to 1871 he was Medical Officer to the Chinese Imperial Maritime Customs at Takao, Formosa, and then until 1883, still under the auspices of the Customs Service, he was in Amoy He had become much interested in filariasis because he frequently saw cases in his daily rounds While on leave in London in 1874–5, Manson searched medical libraries to find out more about this disease He learned that the microscopic immature worms called 'microfilariae', the cause of this distressing malady, had been seen by Demarquay in 1863, by Wucherer in 1866 and 1868, and by Lewis (in urine and blood) in 1872 Full of literature and with a new microscope in his luggage, Manson went back to Amoy in 1876 and proceeded to make a thorough study of filariasis Naturally, he pondered the question as to how the filarial worm could travel from one man to another and cause new infections He finally conjectured that since the larvae of the worm were usually in the blood-stream, they might

escape from their host if removed by blood-sucking insects He decided that mosquitoes were most likely involved because he thought their geographical range coincided with that of the disease

Manson, although a busy practitioner (his patients numbered over 4,000 in 1876), did not stop at mere surmises He proceeded to feed mosquitoes on patients in whose blood were the embryo filarial worms and he noted that the insect could imbibe worms with its blood meal Manson then examined these worms inside the mosquito stomach and he noted that although many died some of the filariae were not digested but actually began to grow He succeeded in tracing the worms as they bored their way through the stomach-wall of the mosquito and entered its abdominal cavity Then the filarial worms moved into the insect's thoracic muscles Concurrently, the parasite increased in size, developing a mouth, an alimentary canal, and other organs Quoting Manson, 'Manifestly it was on the road to a new human host'

Here at last, scientifically observed, was a parasite of man's blood being sheltered by a blood-sucking insect, undergoing essential development, 'on the road' to another human host Manifest indeed were the implications of this discovery, first published in 1877 in *The China Customs Medical Reports* In fact, here was the birth of modern tropical medicine! Manson published again in 1879, using the title, *On the development of* Filaria sanguinis hominis, *and the Mosquito considered as a Nurse* A few scientists accepted Manson's report with enthusiasm but many were cold to it, so the observations were repeated and amplified and republished in 1884 in the Linnean Society's *Transactions*

Unfortunately, although an anonymous reviewer in the *Veterinarian* in March 1883 had suggested that the filarial larva when fully developed in the mosquito might be deposited by the insect as it fed, Manson believed that the filarial worms escaped from the muscle-tissue of drowned mosquitoes into water which then infected those persons who drank it He had placed too much dependence on a

book on natural history which stressed the ephemeral character of mosquitoes, leading him to believe that the insects quickly perished in the water on which they laid their first eggs The fact that mosquitoes could live for several weeks, repeatedly taking blood and laying several batches of eggs, was unobserved by Manson Largely for this reason, Manson did not discover the complete chain of filarial infection from man to mosquito to man This was demonstrated in 1889 by Bancroft in Australia, and by G C Low in England in 1900, with infected mosquitoes sent by Bancroft Incidentally, the latter had written to Cobbold in April 1877, stating his suspicion that mosquitoes were involved in the transmission of filariasis

Other scientists had already reported the interesting fact that certain parasites may have successive hosts, a phenomenon called metaxeny by Ross, meaning the transfer of a parasite from one host species to another As far back as 1790, Abildgaard had discovered that certain parasites lived for a time in fishes and then reached their maturity in the bodies of water fowl which had eaten the fishes Then in 1841–2 Eschricht and also Steenstrup studied the alternation of generations in some *Trematodes*, and Kuchenmeister between 1815–53 made similar observations in certain *Cestodes* About 1858, Rudolf Leuckart discovered living in a small water flea called *Cyclops*, a worm which at one stage of its life is a parasite of fishes This was probably the first instance of a member of the phylum *Arthropoda*, to which the insects as a class belong, being incriminated as intermediate host to a parasite of vertebrate animals Again Leuckart, in 1867–8, observed that a parasite of mice lived for a time in the 'meal worm' larvae of certain small beetles About the same time Melnikoff, a Russian student working with Leuckart, found that biting lice can act as hosts to dog tapeworms Here were the first proved cases of insects acting as intermediate hosts to animal parasites

The first time an arthropod was proved to be host to a parasite of man was when Fedschenko, a Russian naturalist and traveller, prompted by a suggestion of Leuckart in 1858, found in *Cyclops* some embryos of the guinea worm which

escape from their host if removed by blood-sucking insects. He decided that mosquitoes were most likely involved because he thought their geographical range coincided with that of the disease.

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parasitizes man. This was reported in 1869. Fedschenko did not complete the chain of man to *Cyclops* to man.

Then came Manson, in 1877 to 1879, with his observations which marked the first time an insect (mosquito) was proved to act as an intermediate host to a parasite (filaria) of man. Manson's observations gave him logical grounds for theorizing about malaria and mosquitoes and accordingly, by brilliant induction, he formulated a working hypothesis on facts observed by himself or published by others. In his mosquito-malaria hypothesis, stated publicly in some lectures in 1894, Manson reasoned that if mosquitoes could suck worms out of man's blood, they might as easily draw out malaria parasites. He had been impressed by seeing in blood smears the same exflagellation that had been noticed by Laveran and he surmised that the flagella were spores. As such they would be unable to leave the human body by themselves. But the parasites might be taken out in a blood meal by some kind of suctorial insect, most likely the mosquito. He thought, as he had about filariasis, that perhaps the mosquito later died, liberating the spores in water which, if a man drank it, could give him malaria. Quoting Manson, 'Man, I conjecture, may become infected by drinking water contaminated by the mosquito, or, and much more frequently, by inhaling the dust of mud of dried-up mosquito-haunted pools, or in some similar manner.'

Earlier, Carlos J. Finlay in Cuba in 1881 had made a new and brilliant surmise that mosquitoes could transmit the yellow fever pathogen directly from man to man, from a patient to a new victim. Rather surprisingly, this idea of a chain of infection from man to insect to man, came slowly into malaria hypotheses.

In 1889 Flugge, in his treatise on hygiene, stated that malaria might be transmitted by insects as well as by air and water. Then, shortly before Manson published his mosquito theory of malaria transmission, Richard Pfeiffer enunciated in 1892 a logical conjecture of the same sort, based on his own studies with a related parasite. This was a *coccidium* of rabbits and it multiplied in epithelial cells much as the malaria plasmodium does in red blood-cells. The coccidium

once outside the rabbit's body developed a resistant cyst which made possible the transference of the disease to other rabbits Pfeiffer thought perhaps the malaria parasite might have two cycles of development like the coccidium, one being completed outside the human body. He wrote,

The following solution suggests itself, but I bring it forward only as an hypothesis, the justification for which rests in the fact that it indicates a line of investigation It is possible that in the case of the malarial parasite there exists a developmental cycle which completes itself outside the human host, possibly in the body of a lower animal (as, for instance, certain insects) This malarial germ could then be conveyed to man through the air or water or as Robert Koch has remarked to me through the sting of a blood-sucking insect

According to a note in *The Lancet* by its Berlin correspondent in 1898, Koch suggested that mosquitoes probably deposited their eggs on the human body: the malaria parasites probably issued from these eggs and entered man's blood-stream, causing the disease Apparently Koch had suggested several possible ways in which the mosquito might transmit malaria. He told Nuttall that he began to think of mosquitoes in relation to malaria when he was in India in 1883–4 Laveran and Bignami also had ideas about [illegible] germs were inoculated by mosquitoes'.

So there was nothing fantastic about Manson's hypothesis But human nature once more asserted itself and Manson was derided for his speculations His critics, some of them important in the scientific world, called him 'Mosquito Manson', and once in St James's Street, London, derisively tapped their foreheads as he passed their club. Manson cheerfully tapped his own at them and walked on to fame

Smith and Kilborne's Demonstration

Between 1889 and 1893 Theobald Smith and F L [illegible]

This work was first announced in the *6th–7th Report of the United States Bureau of Animal Industry* in 1891, and was published *in extenso* as Bulletin No 1 of this bureau in 1893 Smith and Kilborne had been following a lead given to them by cattlemen who had long believed that ticks were the cause of Texas cattle fever, a belief which had been ridiculed by scientists Some nicely planned experiments demonstrated that ticks do, indeed, transfer the cause of redwater, or Texas tick fever, from one cow to another This study, however, failed to determine the life-history of the causative *Piroplasma* in the ticks and so did not actually prove an alternate generation in the arthropod, but it was a step forward because it was the first demonstration of a protozoan disease of higher mammals transmitted by an arthropod

Manson had paved the way by showing that an insect could take an animal parasite out of man's blood-stream and act as a host to it He failed to show that the insect could directly infect another man with this parasite Smith and Kilborne went farther by observing that a specific pathogen could be carried from one animal to another by ticks Although they did not see the actual parasite within the ticks, yet their experiments did reveal for the first time a continuous chain of infection which included two mammals and an *interlinking arthropod*

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they were walking along Oxford Street, Manson said to Ross, 'Do you know, I have formed the theory that mosquitoes carry malaria just as they carry filariae?' Manson then told Ross about the flagellate bodies He thought the motile filaments were flagellated spores which passed through the wall of the mosquito's stomach into nearby tissues where they developed further Then when the insect died they were liberated in water and in this vehicle subsequently infected man A few weeks after this conversation Manson announced his theory publicly, as described above

Ross returned to India in 1895 determined to put Manson's mosquito theory of transmission to an experimental test He had a microscope and great zeal But otherwise he was not well equipped for such studies He could obtain almost no literature in India on the subjects of malaria or of mosquitoes and he was unaware of the reports of Beauperthuy, King, Finlay, and of Smith and Kilborne He had little knowledge of mosquito structure, physiology, or taxonomy, and no hint as to what kind of mosquito to suspect or as to what form or position Laveran's parasites might take in the body of an insect It has sometimes been forgotten that there was not a good description of *Culex* mosquitoes in English until 1886 and of *Anopheles* until 1896 when, respectively, L O Howard's publications appeared Finally, Ross did not have good staining methods, in fact the practice at that time was to examine unstained blood smears

But Ross approached his problem with intense concentration, commencing on his birthday, 13 May 1895 He started by rearing *Culex* and *Aedes* mosquitoes from larvae Then he fed the adult insects on patients with malaria crescents in their blood Examining the stomachs of the fed mosquitoes, he was able to witness exflagellation, but saw no further development of the parasites and did not guess the significance of the flagella He did, however, consider exflagellation to be a living process and not a 'death agony', as some observers had described it

Ross tried to infect healthy volunteers by having them drink water in which mosquitoes previously fed on malarious

blood, had died By a coincidence, so typical of much early malaria research, the first patient who drank this water came down with malaria But the twenty-one succeeding cases were negative In 1896 Ross put many *Culex* and *Aedes* mosquitoes to feed on patients and then a few days later induced them to feed on volunteers He thought at the time that perhaps the insects carried the parasites from man to man and either dropped them on the skin in defaecation or else inoculated them by skin puncture But he obtained no evidence whatever of malaria transmission Indeed, nothing that Ross did seemed to bring him any closer to his goal A less determined man would long since have abandoned the search and lapsed into normal routine But Ross hung on with a determined grip

Then in April 1897, in the Nilgiri Hills near Ootacamund, Ross for the first time saw with recognition an *Anopheles* mosquito He apparently had had no access to entomological works and he had not learned that there were anophelines as well as culicines and aëdines in the mosquito family But now Ross at long last realized that perhaps he had been using the wrong kinds of mosquitoes So he began to experiment with his new-found 'dapple-winged' insects, which had four dark spots on the wings and had eggs 'like ancient boats' After a good deal of work, involving many mosquito dissections, Ross in Secunderabad in 1897 on 20 August and again on the 21st, saw pigmented malaria parasites from man, growing as cysts embedded in the stomach wall of *Anopheles* mosquitoes (possibly *A stephensi*) The insects had fed exclusively on a patient whose blood contained the crescent shaped gametocytes of falciparum malaria Ross was by now well acquainted with malaria parasites and with the microscopic appearance of mosquito stomachs and was quick to note the unusual foreign bodies He had no doubt that he was looking at malaria parasites of man that were undergoing development in a mosquito These observations by Ross crystallized the mosquito-malaria speculations of centuries! Two days later he wrote the famous poem in a letter to his wife, stating that he had found 'thy cunning seeds, O million murdering Death'

By this time the fact was well established that multiplication of malaria parasites within red cells in the human blood is entirely asexual One parasite simply divides into several small ones, these burst out of the red cell, and, if they escape phagocytosis, they individually enter new red cells where they repeat the process of growing and then dividing But not all the young organisms when they become mature will divide asexually into young forms Some parasites within the red cell develop into distinctive sexual forms called gametocytes These remain undivided and by their characteristic shapes can be differentiated from the asexual forms Those of *Plasmodium falciparum*, for example, look like minute crescents

William George MacCallum, who became a famous pathologist, discovered the sexual phase of malaria parasites At the suggestion of Dr Thayer, MacCallum and E L Opie, as members of the class that in 1897 was the first to graduate from the Johns Hopkins Medical School, had been investigating the haemocytozoa of birds and the pathology of bird malaria Then MacCallum, in 1897 during his summer holidays in Dunnville, Ontario, studied malaria parasites in crow blood and found that the non-splitting forms are actually male and female parasites On his return to Baltimore, MacCallum confirmed this discovery in blood from a woman suffering from aestivo-autumnal fever He watched the process of exflagellation, saw the male gametocyte throw off thread-like flagella, and observed a single flagellum penetrate and thus fertilize a female gametocyte Such mating apparently never takes place while the gametocytes are inside the mammalian host, but it may occur in a drop of blood on a glass slide several minutes after the blood is shed, and, as was soon discovered, it usually takes place in a mosquito's stomach Manson, it will be recalled, in 1894 had noted that exflagellation takes place some minutes after blood is withdrawn from a malarious patient MacCallum's observations, quickly reported to Ross by Manson, were of great importance for they made it clear that malaria parasites have a sexual as well as an asexual cycle of development Ross had seen exflagellation in 1885 but had not

realized its full significance Now the new findings, added to Ross's Secunderabad observation of parasite development in a mosquito, indicated that the mosquito is the definitive host of the malaria parasite

Ross had made real progress Manson was sure that Ross had seen the malaria parasite in the mosquito stomach and in a publication asserted that Laveran, Nuttall, and Metchnikoff agreed with him But, most unfortunately, soon after Ross made his basic discovery in Secunderabad, his superiors, completely oblivious of the importance of his research studies, transferred him to Rajputana, to a place and to duties such that he could not continue his project However, in February 1898, through the influence of Manson and others who recognized the significance of his observations, he was ordered to Calcutta to resume his malaria investigations At that time, 'chiefly on account of the riots caused by Mr Haffkine's anti-plague inoculation', Ross found it impossible to attempt to work with human volunteers Ingeniously, he turned to avian malaria and in his laboratory, he followed the parasite in its development in the blood of sparrows Then he allowed mosquitoes to feed on the birds so that the insects could take gametocytes into their stomachs Careful microscopic examination of the mosquitoes allowed Ross to study the exflagellation, fertilization, and subsequent development of the parasites in the stomachs of the insects He traced the path and the growth of the parasite from the fertilized zygote in the mosquito's stomach to the oocyst on the gut wall Finally, on 4 July 1898, he saw the sporozoites in the salivary glands of the insect

Ross then made his greatest discovery, something hitherto hardly suspected either by himself or Manson He found that the mosquitoes that fed on malaria-infected birds and that had nursed the parasite in its development from gametocyte to sporozoite could infect healthy birds with the sporozoites During July and August 1898, Ross inoculated twenty-two out of twenty-eight birds through the feeding of *Culex fatigans* which had previously fed on infected birds Here was the last link! It was the first proof of

metaxeny, or change of host, among unicellular parasites of animals: bird to mosquito to bird Ross's reports to his Director-General were dated 21 May and 11 October 1898 and Manson's account of Ross's experiments was read before the British Medical Association meeting in Edinburgh on 24 July.

Ross had written to Manson as follows

Calcutta
6th July 1898

Dear Dr Manson,

Let me in the first place felicitate you and the profession on the new Tropical Section & let me wish it every success in the future It is started under the best possible auspices

I hope this letter will reach you at Edinborough If so, it will be opportune, because I feel almost justified in saying that I have completed the life cycle, or rather perhaps one life cycle, of proteosoma, *and therefore in all probability of the malaria parasite* I say almost, because though I think I have seized the final position, I have not yet occupied it with my full forces

My last letter left me face to face with the astonishing fact that the germinal rods were to be found in the thorax as well as in the abdomen Instead of the hard resisting spores we expected to arrive at—spores easily seen & followed—here were a multitude of delicate little threads, scarcely more visible than dead flagella and poured out amongst the million objects which, under an oil immersion lens, go to make up a mosquito I dare say you imagined my consternation I could not conceive what was to happen to the rods

Well, I was in for a battle It was, I think, the last stand—on the very breathless heights of science I am nearly blind & dead with exhaustion!!—but triumphant Expect one of the most wonderful things

The rods were evidently in the insect's blood *By merely pricking* the back of the thorax and letting the milky juice flow into a minute drop of salt solution thousands of proteosoma coccidium rods could be easily obtained The question was what next?

I now divided my insects before dissection between the thorax & abdomen & examined each part separately It was found that the rods were often *more numerous in the thorax than in the abdomen* there were even cases where scarcely one could be found in the abdomen (the coccidia having evidently burst some days previously as shown by their empty capsules), while numbers (4 or 5 in a field) could be detected on teazing up the thorax & head

Here however I was brought up standing Sometimes the rods were more common in the head, sometimes in the thorax I went at mosquito after mosquito spending hours over each, until I was blind & half silly with fatigue The object was to find if possible a place or structure where the rods accumulate, or to discover some further development in them Nothing

On the 4th however, after pulling out the head by its roots (oesophagus etc) from the thorax, some delicate structure dropped out of the cervical aperture of the latter This proved to be a long branching gland of some sort, looking like a coil of large intestine, and consisting of a long duct with closely packed refractive cells attached to it I noticed at once that the rods were swarming here & were even pouring out from somewhere in streams Suddenly to

them, and on bursting the cells the rods poured out of them just as they pour out of the original coccidia

The rods were quite unmistakable, having the tapering, flattened & vacuolated structure peculiar to them They are identified at once & no structures like them exist in the normal mosquito Here they

possess The rods lay within them quite irregularly & motionless except for brownian movement In one lobe almost every cell contained numbers of rods, in other lobes only one or two cells contained them By the attachment of the cells to the central duct, it seems quite easy for the rods to pass on occasion from the former into the latter

Now what was this gland? Will you believe it, I examined two whole mosquitoes without finding it again? What with the scales, the debris of muscles etc, I could not come upon it A third mosquito gave the same result, until I opened up the head itself There was the gland attached by its duct which fed straight into the structures somewhere between the eyes The cells were again packed with germinal rods

I have found the gland now altogether in seven mosquitoes In six of them the cells were packed (especially in some lobes) more or less with germinal rods In the seventh I could find only a small piece of gland, which was free from rods

I still experience, however, the greatest difficulty in dissecting out the gland itself It appears to lie in front of the thorax close to the

head, but breaks so easily in the dissection that I cannot locate it properly. In the second mosquito however there was no doubt, as shown by evident attachment, that the duct led straight into the head-piece, probably into the mouth

In other words it is a thousand to one, it is a salivary gland.

I think that this, after further elaboration, will close at least one cycle of proteosoma, and I feel that I am almost entitled to lay down the law by direct observation & tracking the parasite step by step—

Malaria is conveyed from a diseased person or bird to a healthy one by the proper species of mosquito, & is inoculated by its bite

Remember however that there is virtue in the 'almost' I don't announce the law yet Even when the microscope has done its utmost, healthy birds must be infected with all due precautions

I say one cycle I think it likely there is another I continually observe that only a portion of the coccidia contain germinal rods The rest, I now think, give rise to the black sausage-shaped bodies shown in Plate I, fig 20 of my report, which I believe may be the true spores of the parasite meant either for free life or to infect grubs Oddly enough, in old mosquitoes these bodies also get carried away into the tissues—unless they are some disease of the insect I will attack this next

7th I dissected two healthy mosquitoes this morning & began by dividing the head & anterior third of the thorax from the middle third by means of a razor, and then carefully breaking up the anterior third In both cases the glands were found & their ducts were traced straight into the head thus —

In all probability it is these glands which secrete the stinging fluid which the mosquito injects into the bite The germinal rods, lying, as they do, in the secreting cells of the gland, pass into the duct when those cells begin to perform their function, and are thus poured out in vast numbers under the skin of the man or bird Arrived there, numbers of them are probably instantly swept away by the circulation of the blood, in which they immediately begin to develop into malaria parasites, thus completing the cycle No time to write more

Yours very sincerely

R Ross

Ross was practically at his goal for he had demonstrated the entire life cycle of the parasite of bird malaria, which is transmitted by *Culex* mosquitoes Ross's discoveries transcended Manson's hypothesis and were fundamental They clearly suggested that the parasite of human malaria, closely

related to that of avian malaria must be carried from man to man by mosquitoes The first observation by Ross in 1897 of a cyst of the human malaria parasite in the stomach wall of a 'dapple winged' mosquito, followed by his complete proof of the transmission of bird malaria by *Culex* mosquitoes, made it practically certain that mosquitoes, very likely *Anopheles*, transmit human malaria However, it needed detailed proof and Ross set out to provide it But he encountered initial difficulties and in September he was [illegible]

in Tropical Medicine at the Liverpool School He then went to Sierra Leone where, later in 1899, he confirmed the man to mosquito to man cycle of malaria transmission, which had been proved the year before by Italian workers

The Italian Contribution

Amico Bignami and A Dionisi in 1894 at the Santo Spirito Hospital in Rome tried without success to find out if mosquitoes captured in malarious Fiumicino were capable of producing malaria when they fed on man In 1896 Mendini in his *Guida Igienica di Roma* supported the hypothesis of the inoculation of malaria by mosquitoes Then, in 1898, Giovanni Battista Grassi made extended studies on the mainland and in Sicily to determine whether or not there might be species of mosquitoes peculiar to malarious districts He found three species that seemed to be confined to such areas One in particular was *Anopheles claviger* Fabr (*A maculipennis* Meigen 1818—perhaps *labranchiae*) which seemed to be abundant in the most malarious places and which Grassi observed to attack man as well as animals

The Italians were now hot on the scent Grassi and Celli, for example, had been much impressed by Theobald Smith's reports and they learned promptly of and gave full weight to Ross's proof of the transmission of avian malaria So it came about logically that in September 1898 Grassi collected *Anopheles* mosquitoes in the highly malarious area

of Maccarese and took them to the Santo Spirito Hospital in Rome, some forty miles distant Here Bignami liberated them in the room of Abele Sola, who had been a patient in the hospital for six years and who, as ascertained by careful history-taking, had never had malaria The mosquitoes fed on the volunteer and on 1 November he had a chill, thereafter developing clinical malaria of a 'primary aestivo-autumnal infection', with positive blood smears Sola had a severe attack followed by several relapses Bastianelli, Bignami, and Grassi in December 1898 and January 1899, carried out successfully three similar experiments, and these four controlled mosquito inoculations were the first of the kind ever made They were so decisive that no reasonable doubt remained, although, because the volunteer patients had lived in a malarious country some observers believed that the negative malaria histories could not be completely certain

But Bastianelli, Bignami, and Grassi were also busy following the parasite in its development in the mosquito On 28 November 1898 these observers were able to report to the *Accademia dei Lincei* their demonstration of the development of human malaria parasites on the gut wall of *Anopheles claviger* They had clearly extended the avian work of Ross to human malaria and in 1899 they were first to observe the complete life-cycle of falciparum parasites in an anopheline mosquito Soon afterwards, Bastianelli and Bignami were first to make the same observations with vivax parasites and then with the quartan species They were also first to confirm Ross's finding that *Anopheles*, not *Culex* or *Aedes* mosquitoes transmit human malaria Grassi, Bignami, and Bastianelli also demonstrated that two other *Anopheles* species—*superpictus* and *bifurcatus* were capable of transmitting malaria parasites The Italian studies were summarized in classic monographs by Marchiafava and Bignami and by Grassi The latter's microscope slide preparations were undoubtedly by far the best of the kind at the time

To Italian workers must go great praise for applying Ross's avian discoveries so quickly to human malaria

Shryock notes that, just as the work of Theobald Smith and Ronald Ross had stimulated the Italians, so in turn the Italians, through the medium of William S Thayer, when he returned to Johns Hopkins from a visit in Italy, stimulated Walter Reed and his colleagues, who made the next great advance in the field of medical entomology, by disclosing the *Aedes* mosquito vector of yellow fever

But to Ross is due, for all time, the credit of being first to place a scientific finger on mosquitoes as the agents that spread malaria from man to man This work brought him a Nobel prize in 1902, and later a knighthood from his king

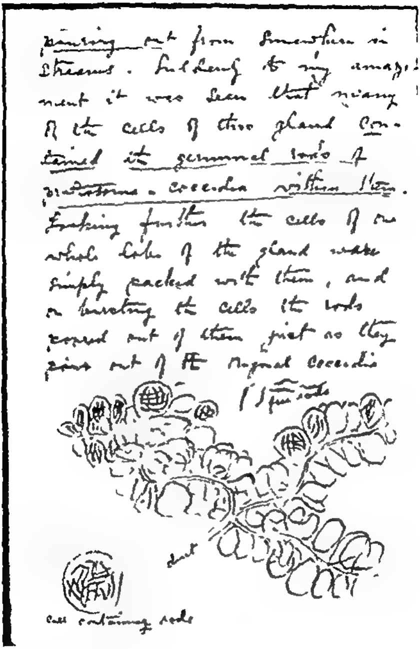
Dramatic confirmation of the fact that malaria is transmitted by *Anopheles* mosquitoes was furnished by Manson in 1900 in two simple tests The first experiment was in charge of Doctor George Carmichael Low, creator in 1907 of the Royal Society of Tropical Medicine His companions were L W Sambon, the artist Signor Terzi, and an Italian servant The three experimenters were all from the London School of Tropical Medicine Together, from early July to 19 October, they lived in a wooden mosquito proofed hut, prefabricated in England and erected at Fumaroli in the Roman Campagna near Ostia The doors and windows of the hut were protected by wire gauze and the beds were provided with mosquito nets By day the men went about the country-side collecting mosquitoes and studying malaria Every night, from an hour before sunset to an hour after sunrise, the party remained within the screened hut In those times, if one slept for a single night during the season in this locality without protection from mosquitoes, malaria was almost certain to result Throughout the area, farmers and Red Cross workers were fever-stricken but the three men in the screened hut escaped While the fact that they had no malaria was not absolute proof of its mosquito-borne nature yet, because their neighbours in unscreened houses suffered severely from malaria, the experiment was highly suggestive and was reported in scientific periodicals and in newspapers throughout the world

In the second and more scientific experiment, some infected *Anopheles* were sent by Professor Bastianelli from

Italy to London, where there was no malaria These mosquitoes had fed on a malaria patient in Rome Manson's son, Patrick Thurburn Manson, a healthy young student, allowed himself to be bitten by three lots of these mosquitoes and fifteen days later he developed tertian malaria The experiment was repeated by George Warren, laboratory assistant at the London School of Tropical Medicine Some mosquitoes were still living after Manson's son fell ill, and, quoting Manson, Warren 'thought it would be a pity to waste them, so he fed the insects on his own arm' He came down with tertian malaria fourteen days later Both volunteers fortunately responded well to three months' quinine therapy and recovered without serious after effects Young Manson had two relapses in 1901 He was killed in an accident on Christmas Island in 1902

But some parts of the malaria puzzle remained to be fitted into place It very soon became apparent that although *Anopheles* and only *Anopheles* transmit malaria, yet the presence of anopheline mosquitoes cannot be taken as an indication that an area is malarious Stephens and Christophers in Bengal and James in Madras noticed this in 1902 Celli in Italy in 1910 stated categorically that 'the geographical distribution of anopheles cannot be made to coincide with the map of malaria' Watson, beginning his classic malaria-control activities in Malaya in 1901, was the first to tailor his field-measures against mosquitoes to fit only those species of *Anopheles* that were harmful Darling in Panama also emphasized the need for a well-centred attack Swellengrebel in 1920 clearly expounded this thesis that only particular species of anophelines by virtue of their susceptibility, their blood meal preferences, and their close contact with man can be malaria vectors The method, originated by Watson, of focusing an attack upon the guilty insects was termed 'species sanitation' by Swellengrebel, and later called 'species control' by Darling, and it remains a fundamental principle in malaria prophylaxis

However, there still were observations that seemed unexplainable, even granting the differences in the abilities of various species to transmit the disease For instance, there



pouring out from somewhere in
streams. Suddenly to my amaze-
ment it was seen that many
of the cells of this gland con-
tained the germinal rods of
zygotomeric coccidia within them.
Looking further the cells of one
whole lobe of the gland were
simply packed with them, and
on bursting the cells the rods
poured out of them just as they
pour out of the original coccidia

A (p 6)

FIG 7 Photograph of pages 6 and 12 of a letter written by Ronald Ross to Patrick Manson, 6 July 1898, from Calcutta, telling of Ross's discovery of sporozoites in the salivary glands of a mosquito and of their significance

Letter in the Ross Archives property of the British Nation Photograph by courtesy of Mr C C Barnard Archivist and Professor G C Macdonald Director of Ross Institute

was the enigma of why so often in Europe the prevalence of malaria seemed to have no correlation with the density of a supposedly proven vector Why was malaria still so prevalent in the Roman Campagna, where it was undoubtedly transmitted by *Anopheles maculipennis*, and yet so rare around Viareggio in Tuscany where there appeared to be an even greater density of the same *Anopheles maculipennis*? Celli and Gasperini had called attention in 1901 to the disappearance of malaria from parts of Tuscany where anophelines remained abundant Bonservizi in 1903 had suggested that attraction of well-stabled domestic animals brought about a dissociation between man and the mosquito in some places Swellengrebel in Holland in 1924 had observed that some of the local *Anopheles maculipennis* did not hibernate Van Thiel in 1926 noted that these non-hibernating forms had shorter wings than the others Here was a clue that suggested races of *maculipennis* Then Missiroli and Hackett, in 1930, using a precipitin test, found that the anophelines taken in houses often contained animal blood Resting place was not a reliable clue to type of blood meal These observers also showed that the amount of malaria in a community was proportionate to the degree to which the local anophelines fed on man Finally, in 1931–3, Missiroli, Hackett, and Martini found the key to the enigma when they discovered that *A maculipennis* is not one homogeneous species What had been called a species was actually a complex of species, not all of which were effective vectors of malaria

Falleroni in 1924 had noted that although the eggs of *maculipennis* showed diverse patterns, the same female always laid the same kind of egg He noted five types of eggs but classified them all as either dark or grey and called them *messeae* and *labranchiae* after two friends in the Health Department—Doctors Messea and Labranca Martini, Missiroli, and Hackett, following this lead, were able to differentiate at least six varieties, differing more in biological than in physical traits First, Swellengrebel and his colleagues in Holland and then Corradetti in Italy in 1934 observed in cross-mating experiments a mutual sterility

which was additional confirmation of the existence of several species within the complex. All these observations had fundamental importance, for it became possible to separate the usual vector—*labranchiae*, from the non-vectors in the *maculipennis* complex and so to explain why there could be a high density of anophelines in an area devoid of malaria.

Recently in Pavia, in Professor Carlo Jucci's laboratory, Professor Frizzi has demonstrated that *maculipennis* species differentiation is also possible by means of the characters of the giant chromosomes in the salivary glands of fourth stage anopheles larvae, an observation that is likely to be of help in untangling other *Anopheles* complexes hitherto troublesome in other parts of the world. However, I do not want to imply that the confusing question as to exactly what constitutes a species has yet been completely answered. To a considerable extent one must still say that, 'A species is what an authoritative taxonomist says is a species.'

Thus one aspect and then another of the complex epidemiology of malaria has been explored. Hippocrates pointed to environmental factors and many observers have been spelling them out ever since, so that today the specific factors involved in many areas are well known. Parasite and mosquito incidence and prevalence can now be surveyed and measured in several helpful ways. Dempster, in 1847–8, pointed out the usefulness of spleen surveys to locate malarious communities and there are now many malariometric methods and indexes of value. Recently there has been progress in evaluating the several variables involved in the spread of malaria, a subject of great interest to Ronald Ross. Professor George Macdonald, Director of the Ross Institute at the London School of Hygiene and Tropical Medicine, has been able further to develop Ross's formulae and thus to make clearer the complicated interplay of man–mosquito–parasite in the rise and fall of endemic and epidemic malaria.

4

HIDDEN PLASMODIA

An authoritative treatise on tropical medicine in 1922 described the early life-history of the malaria parasite in man in the following words

> Once in the blood stream, the sporozoite quickly attaches itself by its anterior end to the edge, or side, of a red blood cell, into which it gradually penetrates by means of peristaltic contractions, combined with active lashing to and fro of the whole body The time taken for complete penetration is from 40 minutes to an hour

T[illegible] was buttressed by a cor[illegible] sporozoite with one end buried in a red cell, the other end obviously eager to follow It was the usual story, repeated in all textbooks on the august authority of Professor Fritz Schaudinn, who published in 1903 an eye-witness account of the penetration of red corpuscles by vivax sporozoites, newly released from the salivary glands of a mosquito What Schaudinn actually saw remains a mystery His assistant, Max Hartmann, told Professor Reichenow some years later that in the Rovigno laboratory he had been called to the microscope and he saw what Schaudinn described and, we now know, obviously misinterpreted

The life-history of the malaria parasite in *Anopheles* had been thoroughly confirmed—from gametocytes as taken into the mosquito gut with the blood of an infected patient, through sexual development in the insect's gut, growth of oocyst on the stomach wall, and finally lodgement of hundreds of sporozoites in the salivary glands ready to infect human victims when the mosquito obtains its blood meals Grassi in 1901 had described these stages of malaria parasite development in mosquitoes so accurately that later research has yielded little of additional importance

So, too, once the parasite appeared in the erythrocyte in

human blood, its subsequent development and division into merozoites which will infect other red cells, or into gametocytes which will infect mosquitoes, was well known and amply confirmed. But between the time the insect injected the sporozoites and the time the erythrocytic forms appeared there was a mysterious hiatus, several days long. During this prepatent period no parasites have ever been seen in red blood-cells. Boyd and Stratman-Thomas in 1934 demonstrated that blood taken from a patient infected with vivax sporozoites was not infectious to others for seven days, after which time-interval parasites had appeared in the red cells and the blood was infectious. Schaudinn's simple story had been retold for thirty years, although students of malaria were not happy about it. Probably a majority—including myself—made determined attempts to observe a sporozoite penetrating a red cell, but always without success.

Not only was failure to confirm Schaudinn's report universal, but other points also were suggestive of unsolved mysteries. For example, consistent clinical and chemotherapeutic differences existed between an attack of malaria caused by injecting infected blood taken directly from a patient, and an attack due to the injection of sporozoites from or by an infectious mosquito. Yorke and Macfie in 1924 clearly described the fact that blood-inoculated malaria, in which no sporozoites at all were involved, was much easier to cure than that produced by the same strain of parasite inoculated in the sporozoite stage. James, in 1931, on the basis of these differences suggested the hypothesis that sporozoites, immediately after entry into the human body, proceeded to reticulo-endothelial cells or to cells lining the capillary blood-vessels. He stated that in such cells the parasite might have an incubation period to prepare it to enter red cells. Ruge in 1936 put forward a similar suggestion. These theories accounted for the mysterious time-interval between inoculation of sporozoites into a man's blood by a mosquito and the first appearance of infected red cells as seen in a blood smear some days later. They also suggested that parasites not located in red cells may be less accessible to drugs. Moreover, such forms

may be concerned with relapses Warren and Coggeshall in 1937 observed in avian malaria the same sort of latent period during which the blood was non-infectious They proved that during this time the parasites were in the spleen, liver, and bone marrow, all of which were infectious on injection into other birds

The fact that parasites were completely absent from the blood-stream during the prepatent period was made crystal-clear by Fairley's classical experiments in Australia, during the Second World War, reported in 1945–7 He demonstrated conclusively that after the infection of volunteers by mosquitoes, the sporozoites circulated free in the blood-stream only for about half an hour Then they vanished Thereafter, for six days in the case of *P falciparum* and for nine days in the case of *P vivax*, large amounts of blood taken from an individual known beyond doubt to be infected, did not give rise to infections in other volunteers But after the latent period had passed, parasites duly appeared in the blood-cells and proceeded to exhibit familiar and characteristic development at the expense of the corpuscles Now the blood was, of course, fully infectious to volunteers

No doubt remained about the initial disappearance of the parasites But where did they hide? As early as 1893, Golgi had suggested that unpigmented forms of *P falciparum* which he had seen in endothelial cells, represented not only an early phase of development but also a source of relapses and a stage in which the parasite could resist antimalaria drugs Grassi, in 1900, advanced the view that the malaria parasite first entered tissue-cells where it passed an intermediate stage before penetrating the blood corpuscles But because of Schaudinn's report, neither Golgi nor Grassi pursued these ideas, now known to have been close to fact

The first tissue-cell malaria parasites to be seen were found, not during the mysterious incubation period but in a later stage of the infection, when red cells had already been invaded It appears that MacCallum in 1898, Anschutz in 1910, and Ben-Harel in 1923, among others, had observed such tissue forms without recognizing their significance

Huff, in 1930, noticed the abundance of parasites of *P elongatum* in red cell precursors of the haemopoietic tissues and, *in 1935*, Huff and Bloom described and portrayed forms of this parasite in all cells of the lymphoid and myeloid series Raffaele in 1934 described tissue forms and in 1936 suggested that sporozoites of this species (*P elongatum*) continued their development in endothelial cells In 1936 Raffaele also found these tissue stages in a second species of bird malaria (*P relictum*)

James and Tate in 1937 found characteristic tissue forms of the parasite in still another avian malaria (*P gallinaceum*) and in 1938 they proposed the term *exoerythrocytic stage* for the unpigmented schizonts which they had found in tissue-cells This name, frequently abbreviated to 'E-E forms' has now been widely accepted

The term exoerythrocytic was applied and still applies to any form of the parasite found in cells other than red blood corpuscles, either early or late in the infection Thus far we have been discussing the later stages found concurrently with the red-cell forms But we now come to the discovery of the parasite in its tissue development before red cells have been invaded For these early stages the word *pre-erythrocytic* is used The discovery of such pre-erythrocytic tissue stages of the malaria parasite was made in 1940 in *P gallinaceum*, independently by Lily Mudrow in Germany and by Shortt, Menon, and Iyer in India Reichenow and Mudrow in 1943 gave detailed descriptions of these forms in the avian *P relictum* Then, in 1944, Huff and Coulston in Chicago described for the first time in great detail the full cycle of development of the avian malaria parasite, *P gallinaceum*

In 1937 Raffaele reported finding exoerythrocytic forms in bone marrow of patients infected with *P vivax* and *P falciparum* The next, and very important step, was taken by Shortt and Garnham in 1948 after three years' study of this problem Over 500 heavily infected *maculipennis* mosquitoes were persuaded to feed on a monkey Then these mosquitoes were ground up with their myriads of sporozoites and were injected by needle, half into the monkey's muscle-tissue and half into its peritoneal cavity, a truly

enormous inoculation of infectious sporozoites The monkey was killed on the seventh day and various tissues removed for microscopic study After a meticulous search, Shortt and Garnham reported the pre-erythrocytic form of this mammalian malaria parasite, *P cynomolgi*, in the parenchyma cells of the liver A second monkey similarly inoculated was killed on the sixth day and again the pre-erythrocytic forms of *P cynomolgi* were found in liver-cells These were momentous findings Later, in other monkeys killed three and a half months after the start of the infection, exoerythrocytic forms were still in evidence, probably the source of characteristic relapses

The monkey parasite, *P cynomolgi*, closely resembles *P vivax* of man So it was logical to assume that what had happened in the monkey might also happen in man But it needed proof and this had to be found in man There must be a courageous volunteer who would be willing to accept not only a malaria infection but also an operation in which some liver-tissue would be removed for microscopic examination Such a plan also required courageous investigators, for it is not a light responsibility to sicken a man with malaria and then subject him to a major operation

An experiment was set up through the co-operation of Shortt and Garnham of the London School of Hygiene and Tropical Medicine and Covell and Shute of the Ministry of Health's Malaria Laboratory at the Horton Hospital for Mental Diseases, Epsom The volunteer was a patient who had been given a malaria infection 22½ months previously as a therapeutic measure and had had thirteen peaks of fever at that time, with considerable benefit He and his wife gave full consent for another infection plus the operation for removal of liver-tissue After careful preparation, it was possible to induce no fewer than 2,010 presumably infected *Maculipennis atroparvus* mosquitoes to feed on the volunteer Then 200 salivary glands dissected out from these mosquitoes were injected into the patient's vein Despite the enormous dose the patient did not develop a clinical attack nor were parasites found in his peripheral blood, which must have retained a strong immunity from the previous

infection with the same strain of plasmodium Neverth
as subsequent events proved, this man had been infect

The operation for removal of liver-tissue was mad
the seventh day and the patient made an uneventful reco
Then came the difficult but thrilling microscopic searc
pre-erythrocytic parasites in the liver-tissue Because
experiment had been nicely based and timed, and bec
of the unusual degree of co-operation in planning, in
paration of mosquitoes, in surgery, and tissue examina
the search was successful Shortt and his colleague
March 1948 reported pre-erythrocytic stages of the hu
malaria parasite, *P vivax*, in liver parenchyma
exactly as predicted Here, sixty-eight years after the
covery of the human malaria plasmodium, was the ke
the mysterious incubation period!

It was demonstrated by these observers that the
erythrocytic cycle of *P cynomolgi* persisted in the liv
monkeys after the establishment of the infection in the
cells of the peripheral blood and still later, after the eryt
cytic forms could no longer be found It was these
exoerythrocytic forms which were the probable cause o
well-known relapsing tendencies of the parasite S
relapses appear to originate in exoerythrocytic stages w
have lain dormant in liver-cells

As already mentioned, the work of Fairley had ma
entirely clear that in *P falciparum*, as well as in *P vi*
there was a cryptic or prepatent phase following inocula
of man with sporozoites So, now that the pre erythroc
forms had been found in vivax malaria, there seemed l
doubt that in falciparum malaria also there must be s
stages But it needed proof Shortt, with the co-opera
of Fairley, Covell, Shute, and Garnham in 1949 set ou
obtain it

Once again a volunteer was needed and this time
found in the person of Mr C H Howard, who, on his
initiative and cheerfully, offered himself for the advar
ment of scientific knowledge, in the hope that his ac
would eventually benefit others A man of stout heart
noble spirit, he allowed himself to receive in a short sp

of time the bites of 770 mosquitoes, heavily infected with *P falciparum* The strain of parasite used had been obtained through the courtesy of Professor Ciuca of Bucharest That this parasite was active and typical had been proved by infections in four patients whose type of mental disease was benefited by malarial fever

On the sixth day, 140 *hours after infection*, a small piece of Mr Howard's liver was excised at operation Following removal of the liver-tissue, came the exciting and exacting business of preparing microscopic sections and searching them for the pre-erythrocytic parasites These were found, as predicted, and thus another notable land mark had been established by Shortt and his colleagues Once again, the same nicety of planning and effectiveness of co-operation, so prominent in the *vivax* study, were outstanding It is pleasing to report that Mr Howard's convalescence was uneventful and that the malaria attack which he suffered was completely cured with chloroquine So thanks to public spirited volunteers, and to the intelligent skill and, I would emphasize, the courage of a group of British scientists, the last major pieces of the puzzle appear to have been fitted into place

Covell reported an interesting sequel to Mr Howard's experience *Some months after the experiment he developed* a perforation of a duodenal ulcer The surgeon who operated in this emergency stated that the previous operation on the liver had produced adhesions that had sealed off the site of the subsequent perforation and that quite likely had prevented a general peritonitis—a sort of reward for services rendered!

The first confirmation of the finding of exoerythrocytic stages of *P falciparum* in parenchyma cells of the human liver was in 1952 by Jeffery, Wolcott, Young, and Williams in the United States Then, in early 1954, Garnham and his colleagues demonstrated similar exoerythrocytic stages of *P ovale* in another human volunteer These early forms have now been revealed in *P inui* (which closely resembles *P malariae*) and *P cynomolgi* of monkeys, and in *P vivax falciparum* and *ovale* of humans, as well as in several avian plasmodia

Finally, we may take brief notice of attempts to cultivate plasmodia. As mentioned previously, one of the reasons for early scepticism about Laveran's parasite was the difficulty in isolating it in culture. Numerous attempts were made between 1880 and 1912 but no one was successful in obtaining more than a slight prolonging of the survival time of the organism. The first serious claim to have obtained reproduction of plasmodia *in vitro* was made by Bass and Johns in 1912. They believed that three successive generations had occurred in their cultures. Thomson and Thomson, using much the same technique, reported four generations in one tube. However, Geiman, who has studied the subject most fully, believes that it was not proved by either pair of investigators that new generations had actually developed *in vitro* in their experiments. Since 1941 the work of Trager, and particularly of Geiman and colleagues, as well as others, has resulted in culture techniques that beyond doubt do produce multiplication of plasmodia *in vitro*. The results are still far from being as satisfactory as from bacteria cultures, but they do provide some help in malaria studies. Thanks largely to the work of Hawking it is now also possible to obtain multiplication of exoerythrocytic stages in tissue cultures.

So there has been great progress aided by many workers in many lands. The marsh miasmata have slowly taken rational form as vector species of *Anopheles* mosquitoes: the febrific poison has been revealed as a protozoan parasite with a sexual stage in its definitive host, the mosquito, and an asexual development in certain tissue- and blood-cells of its intermediate host, man: the plasmodium has been followed, with but a short hiatus of a day or two, from the insect's beak into man's innermost tissues, into his bloodstream, and finally back into a mosquito.

At last, the pestiferous demons of the ancients, the 'invisible animals' of Varro's marshes, the mysterious 'particles' of Fuller and the 'stupendous agencies' of Bartlett have been 'sized, figured, and situated' and are now highly vulnerable to attack.

SECTION II

THE UNRAVELLING OF MALARIA THERAPY

THE medical historian Baas wrote that,

> An acquaintance with the views and the knowledge of epochs of time, frees the mind from the fetters and currents of the day, with its often oppressive restraint, widens the horizon for a glance into the past, and an insight into the present of human activity, deepens the view for a comprehension of the ideas which guided the earlier and the more recent physicians, and gives, on the other hand, to our daily professional labour a higher consecration, by inserting it as a most useful and necessary link in the chain of development of past and future humanity The significance of the work of the individual, and his true value and true position with regard to all humanity, are first revealed to us clearly in and through history

One does indeed gain orientation and stimulus in studying the past As Andrew Balfour once said, 'There is nothing to compare with the historical perspective as a means of adjusting our ideas, of clarifying our conceptions, of stimulating our flagging energies' So we have been encouraged to continue this retrospect of man's conquest of malaria, hoping that it will have value in the days ahead when our gains must be extended and consolidated

Our first lecture dealt with the unfolding of those once-hidden agencies that cause and spread malaria Now we shall attempt to unravel a little the tangled skein that from early days to the present time symbolizes man's attempts to treat malaria

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5

PRE-CINCHONA PERIOD

Prehistoric Therapy

In the beginning, malaria treatment probably consisted of solitude and self-care. These are animal reactions to disease and disability and were doubtless also those of earliest man. There is evidence, however, that at least 20 millenia ago, Cro-Magnon tribesmen began to practise the humane principle of administering treatment to those who were ill. The early practitioners are sometimes referred to as 'medicine-men', but they appear to have had no medicines nor any knowledge of pharmaceutical matters. Their ministrations were attempts to circumvent or to cast out the spirits of disease by what we now call sorcery and magic, methods that to them must have seemed logical enough.

Involved in the practice of magic have always been two basic ideas, or laws, (1) of similarity, and (2) of contagion. To the untrained mind, circumstances or objects closely similar in form, colour, or sequence most likely are basically related. For instance, a cold frog, after suitable incantation, might be expected to carry away from a patient the chills of malaria. Secondly, objects that have been in contact or juxtaposition are presumed to continue to affect each other no matter how far removed they become. Nail parings, for example, must not be left accessible to any enemy because, by heating them, he might cause a fever in the person from whom they were cut. Excrement must be buried, not for hygienic reasons but to circumvent the contagion of magic.

Slowly, and quite likely through the efforts of the older women, various herbs, leaves, barks, roots, and minerals gained favour for the cooling of fevered heads and the relief of bodily chills. The number of such therapeutic substances became ever larger down through the ages;

indeed, active search for new antimalarials continues to the present day

Early Historic Time

In early historic time there appeared another line of therapeutic approach Men began to attribute to gods the power of driving out disease-causing devils and spirits Moreover, it seemed reasonable that disease might come as punishment for violations of principles established by the gods So that treatment began to include both exhortation and penance Spiritual aetiology indicated spiritual therapy, ideas of religious causation led to the priest-physician But along with attempts to rout devils by noise, trick, exorcism, and prayer, and added to the white magic and protective amulets, the propitiatory offerings and sacrifices, there came to be also increased reliance on a *materia medica*

The medicinal substances were usually prepared or administered in accord with rules which reflected spiritual or religious convictions Herbs were gathered by specially designated persons, at set times, and under prescribed conditions A bark should be taken from the eastern side of a tree, a root approached only from the right, then circled three times and pulled out of the earth slowly, as an appropriate *incantation was recited*

Babylo Assyrian therapeutic practice, for example, involved much ritual, especially in regard to water, which was considered to be the sacred element of the god *Ea* The clinical methods of the Babylonian physician were designed principally to appease or circumvent the gods and to expunge disease devils from a patient by magical rite, sacrifice, and prayer In ancient Egypt there was not only practice of magic by a corps of priest-physicians but also much reliance on drugs For instance, more than 700 remedies are mentioned in the Ebers Papyrus of 1550 B C Both Babylonian and Egyptian therapy included at times concoctions aimed, like our modern antimalarials, at the pathogen, in those days often visualized as a demon These 'specifics' as a rule were incredibly nasty mixtures designed to induce the disease-producing invader, presumed to have

a weaker stomach than the patient, to leave as quickly as possible. Occasionally, the medicine was honey and cream and sweet-smelling herbs offered as a bribe to persuade the evil spirit to depart.

The Egyptians also had many curative and preventive amulets and precious stones, some of which remained popular for centuries. But among all the Babylonian and Egyptian potions, electuaries, gums to be chewed, gargles, snuffs, inhalations, salves, plasters, poultices, injections, suppositories, clysters, fumigants, and nauseous mixtures, there was none that now appears to have been designed for the special treatment of intermittent fevers.

The Chinese from ancient times until the present day have attached therapeutic significance to special colours and shapes of plants and have believed in the doctrine of signatures: for example, yellow flowers to treat jaundice. Devils and spirits, magic and sorcery have also played a large part in Chinese medicine. Hydrotherapy, in the form of a cold bath for fever, seems to have originated in China. It is also of considerable interest that Huang Ti, some 3,000 years ago, suggested the administration of arsenic for the intermittent fevers. These he said were caused by alternating replacement and consequent imbalance of the vital principles, *yang* and *yin*—*yang*, the positive, active, productive, and celestial principle of light, heat, and life; *yin*, the negative, passive, and earthly principle of darkness, cold, and death.

Vedic records in India contain many references to the treatment of fevers. For instance, the Indian *materia medica* listed purified mercury as efficacious. *Nakha*, or the nail of a horse's hoof, is also mentioned. In another reference, *matkuna*, which is bedbug, taken internally was alleged to cure quartan fevers. There is a reference in the *Rig Veda* to the treatment of fevers which goes as follows:

> Healing are the watery billows, water cools the fever's glow,
> Healing against every plague, health to thee brings water's flow.

There were imprecations against demons and enemies, charms for expelling diseases wrought by evil spirits or sent

by the gods as punishment for sin, and incantations to impart health and longevity Amulets and philtres, and other devices of magic were also listed The ancient approach was often along lines that today would be called psycho-somatic

But primitive treatment was not entirely based on magic, on spiritual and religious theories, or on similarities Numerous drugs came into widespread use as the result of observation of their effects in man or animals For example, Indian physicians, like the Chinese, administered arsenic for malaria More commonly, herbs were used Over the centuries there was an accumulation of information about the effects of various roots, stems, leaves, and flowers gathered by rhizotomists and professional herbalists Ceremonial purity in the digging or plucking, as noted above, was a most important consideration In China, as in other malarious countries, certain plants gradually acquired the reputation of being useful to treat chills and fever Of course, some had only psychic value and many were merely diaphoretic *in action, thus giving some general relief* to fever patients But a few contained alkaloids that we now know by laboratory controlled tests have specific although limited effect on malaria plasmodia The Chinese *materia medica* listed such remedies In it, for example, are the root *Ch'ang Shan* and the leaves *Shun Chi* which have for centuries been reputed to cure intermittent fevers Recent studies indicate that these roots and leaves are from the plant *Dichroa febrifuga*, a shrub of the family *Saxifragaceae*, indigenous in Yunnan and Szechuan Provinces Alkaloids, such as *febrifugine*, recently have been isolated from this plant and they do have specific anti-malaria action

Early Greek and Roman Therapeusis

Early Greek therapeusis relied on both Egyptian herbs and locally developed magic Herbal medicine became closely identified with Chiron the Centaur and was often accompanied by invocations to the gods Indeed, the ℞ sign with which the physician to this day begins his prescription for the most modern anti-malaria drug appears to stem from

the pagan symbol ♃, which signified the planet Jupiter It now memorializes the *mumbo-jumbo* of ancient healers

Therapy in ancient Greek and Roman times, aside from its mystical aspects, was to a considerable extent an attempt to aid the body in regaining a balance of the four humours by expelling excessive amounts of one or another, and to counteract undue cold, heat, dryness, or moisture 'Specific' treatment of the intermittent fevers included febrific medicines to combat the chills, frigorific to lower the fever, humectating for the dryness of the skin during fever, and desiccant for the sweats In each class of remedy, four degrees of potency were recognized For example, among the febrific were those (*a*) imperceptible, and (*b*) just perceptible to the senses, (*c*) strongly heating, and (*d*) caustic or burning

Hippocrates, although convinced of certain astrologic influences, rebelled against mystic therapy and repudiated much of the earliest Greek practice He relied more on rest, massage, hydrotherapy, control of diet, and change of residence, for malaria treatment He generally gave purgatives early, sometimes employing cautiously measured doses of hellebore (which today we prefer to restrict to veterinary practice, if used at all) Hippocrates advised hot baths later in the attack, and he might prescribe also trefoil, asafoetida, and wine to increase perspiration He made it a general rule in all intermittent fevers to restrict food during paroxysms Afterwards, he would give his patients nourishing barley gruel or *ptisan*, soothing *hydromel*, or honey boiled in water, or perhaps *oxymel*, which was honey in sour wine or vinegar It is also recorded that Hippocrates recommended infusions of mistletoe for splenic enlargement Finally, he sometimes practised venesection

Celsus, in discussing the treatment of fevers wrote (Book III 4 1–3)

Asclepiades said that it is the office of the practitioner to treat safely, speedily, and pleasantly That is our aspiration, but there is generally
Asclepiades
ith much
frequency but still . . . , but the

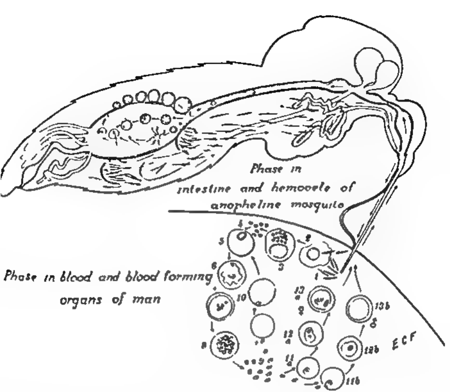

FIG 8 Life-cycle of the malaria parasite showing both intrinsic phase (in man) and extrinsic phase (in mosquito) 1, sporozoites injected into peripheral blood of man, 2–4, exoerythrocytic stages 5–10, erythrocytic stages, 11–13, development of male and female gametocytes

From Clinical Parasitology, 1951, Craig and Faust courtesy of Lea and Febiger Philadelphia

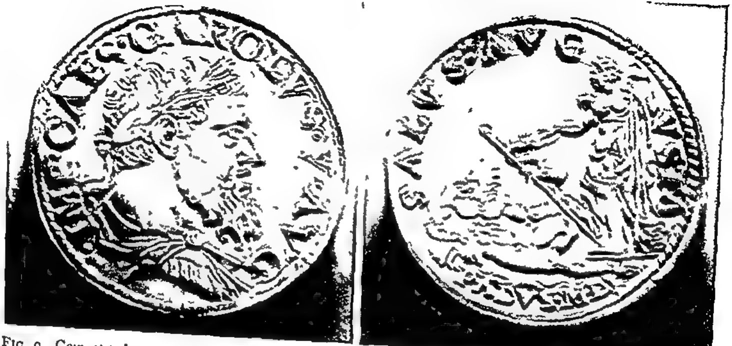

FIG 9 Coin struck to commemorate recovery of Charles V of Austria from paludal fever at Milan, 1550 Obverse, *Imp Caes Carolus V Aug* Reverse *Salus Aug Usta* showing Hygeia erect with staff of Aesculapius sacrificing at altar entwined by *serpent* At left, recumbent river god—the Ticino

Published by courtesy of the British Museum Although many diseases in some aspect or other have been commemorated in coin or postage stamp yet this appears to be the only coin ever struck that refers clearly to malaria In 1952 Algeria honoured Drs A Laveran and L Maillot on postage stamps for their work in malaria *therapy, but* very few other stamps relating to malaria appear to have been issued

actual fever he professed to use as a remedy against itself for he deemed that the patient's forces ought to be reduced by daylight, by keeping awake, by extreme thirst, so that during the first days he would not allow even the mouth to be swilled out Therefore those are quite wrong who believe that his regimen was a pleasant one in all respects, for in the later days he allowed even luxuries to his patient, but in the first days of the fever he played the part of torturer Now in my opinion medicinal draughts and clysters should only be administered occasionally, and I consider that they should not be used as to pull to pieces the patient's strength, since the greatest danger is from weakness (Translation by W G Spencer)

Celsus said that he considered the effects doubtful when Cleophantus 'one of the ancient physicians' poured over the patient's head quantities of hot water and then gave wine to drink In his own writings Celsus paid much attention to rest, hydrotherapy, and diet He also followed the Asclepiades treatment of tertian fever—emetics on the third day, clysters on the fifth, and wine on the seventh

Pliny the Elder was an historian, not a physician, in fact he had a low opinion of the contemporary medical profession He remarked that Romans had done well enough without doctors for 600 years and could probably struggle along without the cult of Aesculapius In one passage Pliny recorded with delight that he had spotted an epitaph reading 'It was the multitude of physicians that killed me' Yet Pliny the layman did not hesitate to give out second-hand advice as to how to treat intermittent fevers In the first century he wrote, 'Any plant gathered from the bank of a brook or river before sunrise, provided that no one sees the person who gathered it, is considered as a remedy for tertian ague, when tied to the left arm, the patient not knowing what it is' Pliny recommended garlic in sour wine for quartan fevers and this may have been the beginning of the popularity of garlic in Italy According to Locy, Pliny also generalized that the longest tooth of a fish would cure a fever

Pepper, sometimes with verbena root, was much used as an antidote for malaria in Greece and Rome It is mentioned by Pliny and by Dioscorides, the Cilician Greek physician

and botanist whose *materia medica* was standard for some 1,500 years. He had travelled widely as a medical officer with Roman legions and as a tourist-collector of herbs. This botanist also recommended cinquefoil (*Potentila reptans*) for milder degrees of malaria—the three-leaved sort for tertian and the four-leaved kind for quartan fevers. Then there was the famous theriac of Dioscorides, containing some sixty-one ingredients and highly esteemed in the treatment of fevers.

Galen's malaria therapy was fairly conservative, although he had a fondness for amulets. As a rule, for the intermittents, Galen administered emetics, diuretics, sudorifics, and cholagogues. He approved of tepid baths, dietary control, and, in certain cases, venesection. Galen's methods were widely followed, as for example by the Byzantines, Oribasius of Pergamos, physician and friend of the Emperor Julian, Aetius of Amida on the Tigris, a Count at the court of Justinian I, and Alexander of Tralles, the last of the great Greek physicians and brother of Anthemius, builder of St. Sophia and the last of the great Greek architects. These writers were all to a large extent compilers rather than originators of anything new in the treatment of the intermittent fevers or other aspects of malariology. Alexander settled in Rome in the sixth century. He held strong opinions about treating intermittent fevers, in this respect getting out of the compiler's rut a little. He did not entirely agree with Galen, especially disapproving of the wormwood used in tertian fevers. He believed in hydrotherapy and regulated diets, particularly in grapes and peaches, and in water-melon given with cold water before a paroxysm. He preferred gentle, not strong, purgatives, and he highly recommended a *rhodomel* prepared from honey, scammony, and the juice of roses; to which he sometimes added agaric and pepper. Alexander was also interested in charms taken eclectically, as Withington has pointed out, from Homer, Orpheus, the Persian Magi, and the Christian Scriptures. For instance, he said that to cure the quartans, patients needed simply to carry about with them some hairs from a goat's chin; or else hang about their necks a live dung

beetle in a little red bag, or instead of a beetle, a green lizard would do, provided the patient's nail parings were also put into the bag

The first and most original of the great Moslem physicians and translators were Hunayn, born in 809 in the country now called Iraq, and Rhazes, so called from his birthplace Rai in Persia Rhazes treated the intermittents with gentle purgatives and cooling drinks, some of which contained sorrel, cucumber, camphor, or other substances He mentioned a soothing mixture of prunes and manna, the latter apparently the dried exudate from some tree, like the manna-ash of Italy He also used emetics Rhazes was a disciple of Galen, and so, unwittingly, is the man who today remarks that he is 'as cool as a cucumber'

Even greater than Rhazes was Avicenna, who was an astronomer, a poet, philosopher, and statesman as well as a [illegible] that the [illegible] rd and [illegible] I soon made great progress, I became an excellent doctor, and began to treat patients using approved remedies At twelve years of age I disputed in law and logic' Avicenna, of course, encountered intermittent fevers In his therapy he cautioned against drastic purgatives and was doubtful about venesection He administered cooling drinks and he considered plums, pomegranates and water-melon to be helpful

Haly Abbas, another great Moslem physician and a Persian, compiled a huge cyclopaedia of medicine founded on Galen, but with some original comment His treatment of the intermittents was conservative and followed Galen and Rhazes Averroes, the last of the great Arab physicians followed Avicenna closely in his treatment of intermittent fevers

From the twelfth to the seventeenth century there were no notable advances in malaria therapy, in fact there seems to have been a decline Increased emphasis was put on supernatural agents of cure, modified by planetary and astrologic notions These were taken over by the Greeks

and Romans from the Chaldeans and passed on into the Middle Ages, when they flourished Even today one comes across some of the same notions in unexpected places

Hippocrates advised his son Thessalos to study arithmetic and geometry because these constituted a basis for astrology and the latter was indispensable to physicians Aristotle believed that the phases of the moon were influential in the course of illnesses Galen thought that he saw a difference in the reaction to disease of those born between the last and the first quarters of the moon and those born between the first and last quarters The second group seemed stronger and less susceptible to infection Ambroise Paré, van Helmont, and Ballonius taught that the full moon period was fraught with additional risk for those who were ill Francis Bacon said that the moon is refrigerant, humectant, and excitant Many other similar views could be cited

The Spider Treatment

Only beware of the fever, my friends beware of the fever!
For it is not like that of our cold Acadian climate,
Cured by wearing a spider hung round one's neck in a nutshell!

Basil the Blacksmith thus welcomes his fellow refugees to Louisiana in *Evangeline* by Longfellow This use of spiders is one of the most interesting of the many nonspecific and often curious malaria treatments As a therapeutic and also preventive remedy it was mentioned by Paracelsus, but it dates back at least to Dioscorides and to Alexander of Tralles The latter wrote of tying up in a rag 'the little *animal that sits and weaves with a view to catch* flies' Alexander's therapeutic cocoon was fastened to the left arm as either a curative or a preventive measure for ague

In the west of England sometimes spiders were imprisoned in a box so that as they wasted away, the ague would depart Sir Kenelm Digby suggested that spiders drew into themselves the contagious air that otherwise would infect a person The venom of the spider was supposed to be derived from poisons that the arachnid had

taken from the atmosphere, even as a sponge soaks up water Black quotes from the diary, 11 May 1681, of Elias Ashmole who testified that, 'I took, early in the morning, a good dose of elixir, and hung three spiders about my neck, and they drove my ague away *Deo gratias!*'

Some considered spiders more effective against malaria if applied as a plaster, and others advised that they be taken internally The garden or Papal Cross spider was considered most helpful Sometimes, the spiders were dried and powdered for oral administration Sometimes they were ingested alive in a pat of butter or submerged in a spoonful of treacle In India the spiders' webs, rolled into pellets, were more valued than the weavers themselves as a cure for malaria Sir Thomas Watson commended this treatment for the intermittent fevers in Madras in 1867 W J Moore disagreed but his note in the *Indian Medical Gazette*, in 1866, was followed by reference to high praise of cobweb as a fever cure by Dr J Donaldson of Madras

Pliny suggested trying the web of the 'wolf' spider applied with the insect itself to the temples and forehead in a compress covered with resin and wax, or the insect itself attached to the body in a reed A Spanish pharmacologist named Oliva in 1882 reported isolating from spider webbing a substance which he called *arachnidin* and which he said had febrifuge properties

Other Curious Malaria Remedies

Other recorded cures for ague include such diverse preparations as the inside of a horse's hoof—said to kill or cure, in either case permanently!—the black snuff of a tallow candle given on sugared bread and butter, a handful of common groundsel worn by the husband or the wife of the patient, yarrow carried in a little bag upon the stomach, a draught of Fuller's teazle (*Dipsacus fullonum*), split pickled herrings applied to the soles of the feet, and 'seven sage leaves for seven mornings fasting'

Transference of disease from man to man, to lower animal, or to plant was often suggested For instance, Black tells of a boy who was suffering from ague A cake was made

of barley meal mixed with some of his urine. This was given to a dog which promptly had a 'shaking fit' with the result that the boy was cured. In Oldenburg, if one were ill of fever, a cure might be effected by setting out a bowl of milk for a dog, and after announcing, 'Good luck, you hound! May you be sick and I be sound!' the patient alternated with the hound in drinking the milk. This ensured transference of the disease. An old Telegu remedy for fever was to embrace a bald-headed Brahmin widow at dawn, thus transferring the disease to her. In New England a patient with obstinate ague sometimes made a string of yarn of three colours, took this secretly to an apple orchard and used it to tie his left hand to one of the trees. Then, slipping his hand quickly out of the knotted string and carefully not looking backward, he ran for his home, leaving his ague in the orchard.

A less humane folk-treatment required the stringing of nine or eleven snails on a thread, saying over each one, 'Here I leave my ague!' Then the snails were burned over an open fire and as they disappeared so did the ague. There was also an East Anglian method. When an ague fit was in progress, the sufferer took a short stick and cut in it as many notches as he had had paroxysms. Then a stone was tied to the stick which was secretly sunk in a pond. If there were no backward glance, and if the string held, the ague chills would cease. A variant of this procedure was to cut several rods, the number depending on the hour when the chill came, e.g. ten o'clock, ten rods. These were burned separately and as each was consumed the patient or the healer repeated, 'As the rod burns, let the ague burn too.'

In Austria, Flanders, and elsewhere, mid-summer fires were sometimes built before a cross. Whoever jumped thrice across the fire would not have fever for a year. In central India, a man with intermittent fever sometimes tried to get rid of it by walking quickly through a very narrow passage, hoping that his illness would fail to squeeze through. In Bohemia a fever patient might be thrown head-first into a bush. If he could get out quickly enough he might leave his illness behind entangled in the branches.

Another European cure was to breathe heavily into a hole in a tree, then seal up the opening, thus imprisoning the fever One who had been relieved in this way was jeered at by a sceptic He took the latter to the tree, craftily opened the hole and thus gave the fever to the doubting Thomas In Hertfordshire it is said that a sure cure for ague was to take the patient to a certain oak-tree, peg a lock of his hair to the tree, then by a sudden wrench leave hair and ague behind on the tree

Innumerable charms have been recorded for dealing with malaria For example, there is a record of one that had vogue among Europeans in the old days in Sumatra It was generally worn about the neck but sometimes carried in a pocket The text read as follows

'When Christ saw the cross He trembled and shaked, and they said unto Him, Hast thou the ague? and He said unto them I have neither the ague nor fever and whosoever bears these words either in writing or in mind shall never be troubled with ague or fever So help thy servants O Lord who put their trust in Thee

Another interesting charm, quoted by Andrews, reads as follows

And Peter sat at the gate of Jerusalem and prayed and Jesus called Peter, and Peter said, Lord, I am sick of an ague, and the evil ague being dismissed, Peter said Lord grant that whosoever weareth these lines in writing the evil ague may depart from them and from all evil ague good Lord deliver us

In Hampshire it is said that ague patients sometimes made three crosses with white chalk on the back of the kitchen chimney, the centre cross being largest As the smoke blackened out the crosses so the ague would disappear

Then there was a common charm to be said up the chimney by the eldest female of a family on St Agnes Eve

Tremble and go!
First day shiver and burn,
Tremble and quake!
Second day shiver and learn,
Tremble and die!
Third day never return

And we must not forget that Serenus Samonicus prescribed for quartan ague a copy of the fourth book of the Iliad placed under the patient's head This was a popular cure for many years Verily, 'Remedies amuse the patient while Nature cures the disease'

We laugh at the prescriptions but not always at those who devised or used them True there were 'the herbalists, water-casters, hawkers of amulets and charms, charlatans, mountebanks, empiricists, quack-salvers, Paracelsians, wizards, alchemists, poor vicars, cast apothecaries, barbers, and good-wives' There have always been impostors, today still surprisingly numerous But for the most part the therapeusis of malaria down through the centuries has been predicated on the supposed aetiology or pathology of the ailment What sort of therapy, indeed, could be recommended today if one accepted Cotton Mather's 1693 ideas on fevers? He wrote, 'And when the Divil has raised those Arsenical Fumes which become Venomous quivers full of Terrible Arrows, how easily can he shoot the delecterious Miasma into those Juices or Bowels of Men's Bodies, which shall soon Enflame them with a Mortal Fire'

Pliny once remarked that in the treatment of quartan fevers, clinical medicine is pretty nearly powerless He therefore listed a number of remedies derived from magicians, including such examples as the dust in which a hawk has bathed itself, tied up in a linen cloth with a red string attached to the body, 'the little prettie snout's end' of a mouse and the tips of its ears wrapped in a red cloth, the animal being set at liberty after they are removed, a dram of swallow's dung in goat's milk, the toe of a horned owl, and other equally weird suggestions

Elgood records that the chiefs of certain Persian tribes near Kerind on the Baghdad–Kermanshah road in times gone by inherited the power to cure malaria by using the bastinado The luckless patient was strung up by his heels when a rigor was noted and was beaten enthusiastically by the chief, who thus assisted the shivering body to generate sufficient heat to drive out the cold

In recent years Nile mud, eggs crushed and steeped in

vinegar, extract of butterfly wings and many other equally unorthodox remedies have been put forward seriously for malaria therapy, and the end is not yet As Macaulay once said 'Nothing is so credulous as Misery', and Oliver Wendell Holmes added 'There is nothing men will not do, there is nothing they have not done to recover their health and save their lives'

In summary it may be said that prior to the seventeenth century the treatment of malaria, apart from dependence on supernatural forces, consisted principally of purging, bleeding, and administering sundry herbs, with some use of rest, massage, hydrotherapy, and control of diet and residence There are also a few early references to mercury and to arsenic as used against the intermittents But whatever the form or combination of therapy, it was so often ineffective against the agues that these fevers were referred to by Sydenham and others as the *opprobia medicarum* However, the course of the intermittent fevers in a goodly percentage of cases is by nature self-limited This inherent characteristic of malaria did and still does lead to the endorsement of impotent drugs Observant clinicians in the past recognized that the disease was not so often cured by therapy as in the words of Sydenham, it was spent by the length of time' Many were content to follow the precept of the Salerno School which taught

> Use three physicians first Doctor Quiet
> Then Doctor Merry man and then Doctor Dyet

6

THE QUININE PERIOD

Cinchona Bark

ALTHOUGH the use of *Dichroa* in China, already mentioned, may have antedated the introduction into Europe of cinchona bark, yet it seems likely that the latter can properly be nominated as the first malaria specific, indeed, as the earliest of any sort in the entire *materia medica* of the West

Cinchona is the generic name of some forty species of evergreen trees of varying heights, up to eighty feet or more, native to the western mountainous regions of South America, from Venezuela to Bolivia, flourishing generally at elevations between 5,000 and 8,000 feet in areas of abundant rainfall About a dozen species of *Cinchona* have been commercially useful because their bark has been found to possess antipyretic properties particularly useful against the intermittent fevers

The first record of successful treatment of malaria by cinchona appears to be that of the case of Juan Lopez, a Jesuit missionary, in Malacotes, Peru, in the year 1600 It is said that he was cured by the 'fever tree' bark given to him by a converted Indian chief Some thirty years later, Don Juan Lopez de Canizares, the Spanish Corregidor of Loxa (Loja), Peru, was reported to have been cured of ague by this same bark, taken on the advice of the missionary *Juan* Lopez

But whether or not the Peruvians had used this remedy before 1600, and, indeed, whether or not malaria itself existed in the Americas prior to the time of Christopher Columbus, are debatable points Some students hold that malaria was a post-Columbian importation and that it was probably implanted in the Americas by the colonists set down by Columbus at Isabella on the north shore of His-

paniola in 1493 Certainly, the environment of tropical and subtropical America was favourable to the spread of malaria and there were plenty of local anophelines ready to co-operate in its dissemination Colonists and, a little later, African negroes provided an abundant source of the seed

Other historians, such as Gualberto Arcos of Ecuador, believe that malaria had existed in the Americas long before the fifteenth century The disease is said to have been rampant in 1378, for example, in the armies of Pachacutec Doctor Jaramillo-Arango of Colombia, who has made a scholarly study of the question, agrees with Arcos He points out that there is much to support the view that the first Americans had their origin in Asia where malaria records clearly go back to very early times and whence migrants could have brought the parasites However, it is said that pre-Columbian documents do not mention the characteristic periodicity of intermittent fevers The early missionaries and *conquistadores* in their chronicles neither affirm nor deny the presence of these fevers But neither do they discuss other diseases known to have been locally indigenous

As regards local use of cinchona bark, several early explorers of the 'Quina Empire' recorded that the natives were strongly prejudiced against cinchona as a medicine Humboldt, for example, declared that Loxans would rather die than take such a dangerous medicine Spruce said he could not convince the *cascarilleros* of Ecuador that their red bark was a good medicine They considered it only useful as a dye Markham reported that the wallets of the native itinerant doctors never contained cinchona bark

But others, earlier on the scene, as William Arcot, a Scots surgeon, de La Condamine, and Jussieu, all recorded that at the times of their visits the use of cinchona bark in the treatment of fever had long been known to the local Indians Bollus, who lived many years in Peru, and who wrote the first detailed account of the use of cinchona in America, definitely stated that before the arrival of the Spaniards, the bark was used for treating fevers Lastres, in his history of Peruvian medicine, states that studies of Inca pathology seem to indicate a pre-Conquest local

knowledge of the curative properties of quina (cinchona) *in malaria*, withheld from the Spanish Perhaps the simple truth is that, as usual, some local tribes did and some did not use the bark as a febrifuge

At any rate, after 1600, cinchona bark was more and more employed by the Spanish in the Americas and by them it was sent to Europe whence its use spread over the world But who first sent or took this medicine to Europe and exactly when or where, are questions still disputed We should like to know the answers because, as Osler said, 'The introduction of cinchona into Europe ranks not only as one of the greatest events in the history of medicine but as one of the great factors in the civilization of the world'

The *traditional* anecdote, dating back many years, appears to have little historical basis It told of the fever (some time between 1632 and 1638) of Francesca Henriquez de Ribera, the wife of the fourth Count of Chinchon, Viceroy *of Peru The Corregidor, Don Lopez, sent to* the count's physician a parcel of powdered bark, the substance that had cured him of 'terciana' The physician, Don Juan de Vega, having tested the powder on a number of patients, is reported to have administered it to the countess with great success Prior to 1639 the enthusiastic Vicereine, or her physician, or some Jesuit father, is said to have sent or carried samples to Spain, where the remedy was referred to as the Countess's Powder This story suffers from the recent discovery of the official diary of the Count of Chinchon, wherein is a careful day-by-day account of the Chinchon *family It now appears that the countess* was blessed with amazing good health Aside from a sore throat and a 'flux and cough on the lungs' she had no illness at all in Peru The noble count himself was frequently ill with malaria, but nowhere is it recorded that he experienced a dramatic cure by fever bark, nor is there any mention of the bark or of the 'Fever Tree' The countess did not take bark back to Europe, for she died in Colombia, on the way home, of what seems to have been yellow fever

It is possible, of course, that some now unknown traveller or navigator was first to bring cinchona bark to a European

port But it appears to be more likely that the first deliberate dispatch of the remedy to Europe was by Jesuit fathers The records seem to show that the first sample of cinchona bark to reach Europe was brought to Rome in 1632 by a Spanish priest, Alonso Messias Venegas, who had made the long journey in order to present a report on the Peruvian Missions of the Jesuits There was living in Rome at the time a famous Spanish priest, Father di Lugo, who in 1643 became the Illustrious Cardinal Juan di Lugo He was a teacher of philosophy in the Gregorian University of the Collegio Romano Apparently, Father Venegas told his countryman about the medicinal qualities of the bark and when Cardinal di Lugo some time later developed a severe attack of malaria he tried the new remedy and experienced dramatic relief Thereupon di Lugo with the authority of Innocent X, requested the Pope's physician, Gabriel Fonseca, another Spaniard, to carry out further trials with the bark In what was probably the first institutional use of this remedy in the Old World, successful tests were carried out in the Santo Spirito Hospital of Rome A highly favourable report led di Lugo to distribute the bark free to the poor who came to his residence During this period arose such names for cinchona as Cardinal's Powder and Jesuit's Bark

In 1649 Cardinal di Lugo, at a General Council meeting of the Jesuit Order, made a powerful plea for the widespread use of the bark especially by the Fathers in their missionary work This resulted in a more rapid dissemination of the new specific throughout the world It may have made possible the curing of the malaria of Emperor K'ang Hsi of China in 1692 with the bark, given by some Jesuit fathers Incidentally, Cardinal di Lugo came from a family of Seville, a town which had almost a monopoly on trade with the western part of South America This fact may have had some effect in increasing the European imports of bark, which started to arrive regularly in Italy from Peru in 1647 The bark was certainly known in Spain by 1639, for there is a record of a cure in that year It seems likely that it was known there even earlier

Haggis states that the earliest mention of cinchona in

European literature was by Herman van der Heyden in 1643 in Belgium. But Baas in his history of medicine states that Pietro Barba, a physician of Valladolid, recommended cinchona in his book, *Vera praxis ad curationem tertianae*, &c. published in Seville in 1642. Some historians also state that an Augustinian monk named Calancha published a religious book in Spain in 1639 which mentioned the bark as a cure for fevers. Another early treatise on cinchona was the *Schedula Romana*, of 1651, a leaflet containing instructions for administering 'Fever Bark', which was to be 'used against quartan and tertian fevers, accompanied by shivers ....' A more comprehensive treatise on cinchona was that of an Italian physician, Sebastiano Bado, in 1663.

The first man to describe the fever tree scientifically was Charles Marie de la Condamine, an astronomer, who in 1735 led an expedition from France to measure an arc of the meridian near Quito, Ecuador, in order to determine the shape of the earth. He had quarrelled with his associates and quit them to explore the Amazon, and eventually the Peruvian country where he became acquainted with the bark and its tree. But the botanical name was given by Carl von Linné, the great Linnaeus who was himself trained as a physician and who had some ideas about water-borne malarial fevers and the parasitic origin of disease. Linnaeus, when he named the fever bark tree 'Cinchona', intended to honour the Countess of Chinchon. Unfortunately, he followed Bado's spelling. The first 'h' was omitted probably because in Italian 'ch' before 'i' is pronounced like 'k', whereas the countess's name in Spanish began with a 'ch' sound, such as plain 'ci' has in Italian. The International Botanical Congress in Paris in 1866 voted to retain this mis-spelling of the generic name of *Cinchona*.

During the seventeenth century there was considerable confusion between cinchona and the somewhat similar bark of a Peruvian balsam tree (*Myroxylon peruiferum*). The latter was the source of a resin much esteemed in ointments for chronic ulcers. The resin was collected as it oozed out of the tree-trunk after slabs of bark had been removed. The bark itself was thought to have some febrifuge qualities,

but actually its effect against the agues was negligible. Yet it became an item of commerce and was the original quina-quina bark. As Haggis has pointed out, merchants began to adulterate balsam with cinchona bark, first because the former was in short supply and secondly because the latter greatly strengthened the antipyretic effects of the balsam. Naturally, this commercial practice did not enhance the reputation of true cinchona bark. Many physicians, unaware that they were using balsam or a much diluted cinchona bark, declared that the Jesuit's powder was a Papal fraud and thereafter refused to have it in their medicine chests.

Nevertheless, demand for cinchona bark increased rapidly and the trees, which grew wild, were recklessly destroyed. Moreover, the hardships of bark-collecting in the Andean forests were of the severest kind, endurable only by the half-civilized Indians and *mestizos*, referred to as *cascarilleros* or *cascadores*, who were employed by speculators or companies located in the towns. The climate was extremely variable, with rapidly alternating sunshine, showers, storms, and thick mist, and temperatures sometimes near the freezing-point. Cinchona trees grew isolated or in small clumps in dense forest. The *cascarillero*, having found his tree, often had to cut away surrounding vegetation and remove the luxuriant climbing and parasitic plants which encircled the trunk. Next, he had to beat the bark as high as he could reach. He then made longitudinal and circular incisions, felled the tree and stripped off all bark. The slabs were dried over an open fire, and the thinnest pieces from smaller branches curled up into tubes or *quills*. The thickest parts were dried flat. Both were packed into bales or put into sacks and transported, usually by the *cascarillero* himself, down the tortuous trail to the market.

Quite naturally it occurred to several scientists that the tree would probably grow on plantations in tropics other than South American. In 1743 de La Condamine attempted to take cinchona plants to Europe but they were swept off his ship by a wave in the River Amazon. In 1849 cinchona trees were planted, but unsuccessfully, in Algeria. The

Dutch, in 1852, sent Justus Charles Hasskarl, a courageous botanist, on a hazardous cinchona-seed collecting expedition which took him across the Andes into Bolivia and Peru. He was successful, by a narrow margin, and from his seeds cinchona cultivation was started in Java in 1854. His government rewarded him with a knighthood of the Netherlands Lion and a Commandership of the Oaken Crown.

In 1860 the British sent out a party under the exceptionally able leadership of Clements R. Markham, a geographer and archaeologist. His collections resulted in cinchona plantings in the Nilgiri Hills of Madras Presidency near Ootacamund, where over 2½ million trees were growing by 1872. This plantation is still a source of government quinine for use in India. Markham was knighted for his achievements.

The seeds and seedlings of these early Dutch and British expeditions were not of the best yielding varieties of cinchona trees growing in South America. The most successful collector of good quality seeds was an Englishman named Charles Ledger, who was a trader in alpaca wools at Tacna, Peru, and, incidentally, who later introduced a flock of alpacas into Australia. Living in the cinchona area, he had learned to differentiate between strong bark and feeble and, knowing of the world market, he sent his West Indian servant, Manuel Icamanahi, for seeds of trees that had bark of high quinine content and that he had seen growing in a certain place. Manuel was gone five years, because four April frosts destroyed the flowers and prevented ripening of fruit of the particular trees that met the requirements. But, finally, he came back with the seeds. Sent out again, it is said that he was seized by Bolivian officials, jealous of their bark monopoly, and although imprisoned, severely beaten, half-starved, and robbed of his possessions, he refused to tell for whom he was collecting seeds and was at last set free, to die soon afterwards of his ill treatment.

Ledger, in 1865, sent fourteen pounds of high-quality seeds to his brother George, who lived in London. George Ledger attempted to sell them to the British Government, who were not interested. However, he finally sold half of

the seeds to the Dutch for a few guilders and the other half to a Madras planter Within eighteen months of this sale the Dutch had 12,000 plants ready to set out and five years later their analyses of bark were showing 8 to 13 per cent of quinine, whereas no other bark at the time being marketed could claim much over 4 per cent The seeds of this species, officially named *Cinchona ledgeriana*, taken to Madras also in time grew well but on a more limited scale The Dutch did a good deal of experimenting with hybrids and successfully developed the world's best cinchona trees Cultivated bark, incidentally, is removed in alternate strips so that the tree is not destroyed Ledger eventually retired to Australia where for some twenty years he received a pension from the Dutch

At the outbreak of the Second World War, Java had some 37,500 acres of cinchona, producing more than 20,000,000 pounds of bark a year The Dutch quinine combine had created what amounted to the most effective crop monopoly of any kind in all history

Use of the Bark

Robert Burton, referring to physicians who attempted malaria therapy before cinchona was available, remarked in 1628, 'A common ague sometimes stumbles them all' We see now many of the reasons why treating the intermittent fevers has been such a gamble even with specific drugs, and why equally capable physicians have opposed each other in bitter debates as to the usefulness of cinchona Confusion between balsam bark and genuine cinchona has already been mentioned, and also obviously, in the absence of effective diagnostic technique there was often failure to differentiate the malarial from other fevers But the handicap also included additional sources of misunderstanding which observations in more recent years have removed For example, it has become clear that not only species but strains within species and, indeed, the successive developmental stages of malaria parasites, vary in their response to the same dose of the same drug Moreover, we have gained some comprehension of the phenomena of relapse, and of

the tissue-cell forms of the plasmodium in relation to treatment. We also realize that the degree of natural and acquired immunity of a patient has profound influence on his response to therapy. Finally, one must add to these complexities the usual difficulties of obtaining systematic administration of any drug and of determining the degree of therapeutic success. It is small wonder that early literature abounds in controversy over the anti-malarial properties of cinchona bark.

For example, the Archduke Leopold of Austria, Governor of the Low Countries, suffered from a quartan fever in the autumn of 1652. He was treated with cinchona by his physician, John Jacob Chiflet, and seemed to have been cured. But when his malaria relapsed a month later, instead of taking more bark he became angry and ordered Chiflet to write a book, in defiance of the Vatican, warning the public against cinchona. This *Exposure of the Febrifuge Powder from the American World*, published in 1653, was warmly welcomed by most physicians; for they agreed that the fever was caused by a harmful fermenting 'principle' which must be expelled from the body by purging, bleeding, and administering emetics, as suggested centuries earlier by Galen.

So there were changing fashions in respect of the use of cinchona. The swinging of the pendulum was well illustrated in India, following introduction of the bark into Calcutta in 1657. At first supplies were meagre and expensive but by the middle of the eighteenth century the new remedy had been popularized by ships' surgeons and it was much used. For example, James Lind in 1765 treated several hundred fever patients in India with the bark and reported having lost in this series only two cases by death, neither of whom had taken much if any cinchona. Lind concluded that, 'In the proper administration of the bark, the cure of ague may be said to entirely consist.'

But during the first half of the nineteenth century, cinchona bark fell into disrepute and disuse in India. The new remedy was replaced by violent purges, large doses of mercury, and extensive blood-letting. This disaster came

about principally through the influence of a single bitter antagonist, a naval surgeon named James Johnson He went to Calcutta in 1804 and by ill luck failed with cinchona to cure his first fever patient After initial doses of the bark the man's high temperature returned, with intense vomiting, jaundice, and death on the third day At post mortem examination Johnson was greatly impressed by the intense engorgement of the liver In his report he does not mention an enlarged spleen or pigment What he saw led him to believe that evacuations and venesection would have constituted more logical therapy His next fever case was accordingly treated by 'brisk evacuations' and repeated bleedings and this man recovered Neither case appears to have been malaria

But thenceforth, Johnson never based his treatment of fevers on cinchona Instead he followed his personal preference for excessive salivation with mercury, purgation with calomel, and blood letting with knife or leech After a brief period in India, Johnson returned to London where in 1813 he published a book entitled *The Influence of Tropical Climate on European Constitutions*, in several editions of which he carried on his crusade against cinchona with 'slaughtering and withering criticisms' Unfortunately, in his few years in India he had succeeded in building up a prejudice against cinchona bark so strong that for a time little use was made of this specific, except that it was sometimes prescribed as a tonic taken in wine after fever had subsided

This state of malaria therapy persisted in India until about the middle of the nineteenth century when the use of cinchona, in the form of the quinine alkaloid, became slowly re established because of the experiences of a physician, Edward Hare, who had arrived in 1839 At first, Hare followed the usual therapeutic practice because, as he said frankly, 'I durst not give quinine, in fact, it was so utterly forbidden by all authorities that it never occurred to me to give it ' But his early results with purgation, salivation, and venesection were so appallingly disastrous that, after reading some old reports by James Lind, he began cautiously to

use cinchona Great success accompanied his new procedure During nine years he treated nearly 7,000 fever patients with cinchona alkaloid and was able to report a mortality rate of less than half of 1 per cent, a notable record at that time The General Hospital in Calcutta then gave cinchona a year's trial and reduced the mortality from all forms of fever tenfold From this time onwards few practitioners doubted its usefulness in treating intermittent fevers

Despite all pitfalls and major setbacks there had been worldwide progress For example, in 1712, Francesco Torti, in Italy, pointed out that cinchona bark was specific only for the intermittents, not for other fevers Torti had experienced at the age of twenty the great honour of succeeding Ramazzini as Professor of Medicine at Modena and he had developed a wide clinical practice which included many fever cases He was first to publish a medical treatise that differentiated clearly the intermittents and his diagnosis was on the basis of their response to cinchona Perhaps Torti's special interest in this subject had been stimulated by his illustrious predecessor For Ramazzini, referring to cinchona bark, had said in 1702, 'surely after the use of this remedy has become known it must be avowed that, concerning the doctrine of fevers and the method of curing them, a change has been made comparable to that which all know followed, *in military affairs, the invention* of gunpowder'

In England, the bark was introduced about 1650 J Rutherfurd Russell states that the following advertisement appeared in the London *Times* of that day, called the *Mercurius Politicus, 'comprising the sum of Foreign Intelligence with Affairs now on Foot, in Three Nations, for the Information of the People'*

From Thursday, December 9 to Thursday, December 16, 1658 The Fever Bark, commonly called the Jesuit's Powder, which is so famous for the cure of all manner of Agues brought over by James Thompson, Merchant of Antwerp, is to be had either at his own lodgings at the Black Spread Eagle, in the Old Bailey, over against Black and White Court, or at Mr John Crook's, Bookseller, at the Ship, in St Paul's Churchyard, with Directions for Use, which Bark or Powder is

attested to be perfectly true by Dr Prujean and other eminent Doctors and Physicians who have made experience of it

Obviously, the bark was not common at that time But by 1677 it had become official in the London Pharmacopoeia under the name *Cortex peruanus* It was well established by the last quarter of the seventeenth century and this came about in no small measure through the ethically questionable but always spectacular practice of Robert Talbor, self-styled 'pyretiatro' or 'feverologist' Talbor made a fortune and achieved a knighthood by exploiting cinchona as a secret remedy Among the famous patients whom he cured of malaria by use of the bark were Charles II, the Dauphin, son of Louis XIV, and in the 1680's the Queen of Spain

In 1682, a year after Talbor's death, the King of France had a book published entitled, *The English Remedy or, Talbor's Wonderful Secret for Cureing of Agues and Feavers* The king had paid Talbor 3,000 gold crowns for publication rights It is of interest that, as Scott has pointed out, one of the formulations listed had the same strength as the present British Pharmacopoeia tincture

Another secret concoction, possibly stimulated by Talbor's success, was prepared by Moises Mendes in 1681 and was called 'Agua de Inglaterra' It was a water infusion of cinchona bark, the precursor of countless 'chill tonics' sold throughout the world during centuries and even today

But, of course, the verdict on the value of the bark was not unanimous The year following publication of Talbor's 'Secret', a Doctor Gideon Harvey issued a *Peculiar Discourse of the Jesuit's Bark* In this he commented, as quoted by Stephens, that

> After all, I could wish these Fathers had kept their Indian bark to themselves, and sure I am hundreds would be on this side of the grave, whose Bones are now turned into their element If you shall meet with a Physician, that can safely and not over speedily Cure you without giving the Jesuit s Powder, never meddle with the Jesuit, with whom the less a man has to do either sick or well, it's the better In fine the effects appear so miraculous to many that they imagine the Jesuits by Imprecation by Exorcisms and Charms on their Bark, have made use of their Cloven footed Master

Added to religious prejudice there was sometimes fear engendered by occasional deaths, for one reason or another, of persons who had recently taken cinchona bark These two factors may have joined to hasten the death of Oliver Cromwell As J Rutherfurd Russell told the story,

In the year 1658, the death of a certain Alderman Underwood, who had taken the bark, made a great stir in London As if an alderman had never died of ague before!—whereas, according to the tables of mortality already referred to, there probably died of ague that year, over England, about 1300 persons, including, doubtless, the normal proportion of aldermen That the death of this alderman, and that of a certain Captain Potter, should be recorded so emphatically as a consequence of ague with *bark*, may be taken as a positive proof that the greatest man of his age did not take bark, although ill of a tertian ague Dr Bates, physician to Oliver Cromwell, describes his fatal illness as 'slow fever, that at length degenerated into a bastard tertian ague' On examination of his body after death, the same authority tells us that the source of the distemper was the spleen, which 'though sound to the eyes', was 'filled with matter like to the lees of oil' Whether Cromwell's life could have been saved by the timely administration of Jesuit's powder, must remain among the questions which can never be answered

Irresistibly one speculates whether or not Oliver Cromwell, at the culmination of his power and glory, may not have been a victim of the religious animosities that he had done so much to arouse Certainly, it seems to be a fact that not one of his physicians dared to administer the 'popish powder' that might have saved his life

For a time, in England and on the Continent, some practitioners esteemed that ancient drug *arsenic* more than the bark as a remedy for the intermittents It seems to have formed the chief ingredient of a much-used patent medicine called 'The Tasteless Ague Drops' In London, Thomas Fowler in 1786 published a *Medical Report on the Effects of Arsenic in the Cure of Agues, Remittent Fevers, and Periodic Headaches* Others joined in praising this mineral that was bitter neither to tongue nor spirit

But in spite of all opposition and competition cinchona bark became ever more firmly entrenched As Castiglioni

and others have noted, it developed into an important factor in the downfall of Galenism that insisted on treating all illnesses with purgatives

In 1696 Conrad Peyer and Michele Bernard Valentini had introduced the bark in Germany where it met with considerable favour Before long it was available in most malarious countries, although sometimes in relatively small amounts

Throughout the seventeenth, eighteenth and first quarter of the nineteenth centuries, the bark was administered in its crude form The dosage varied The Jesuits usually gave about 8 grammes of bark (equivalent to 12 grains of alkaloid) just before a chill was expected Sydenham at first was lukewarm about cinchona but finally used it fairly extensively He preferred an amount of bark equivalent to 48 grains of alkaloid added to about two pints of red wine, divided and taken by the patient in twelve equal doses after the end of a paroxysm, i e after the 'corrupt humours' had been expelled Trousseau and others followed the same plan Not until 1768 was it demonstrated clearly, by the practice of Lind, that bark was most effective when given in full doses as soon as the disease was diagnosed

As early as 1659 Willis pointed out that while bark would cure acute attacks of malaria it would not prevent the relapses Bass quotes an interesting note of advice sent by Benjamin Franklin to Samuel Johnson, a New England divine who had had fever and ague 'Don't imagine yourself thoroughly cured and so omit to use the bark too soon Remember to take the preventive doses faithfully' This important shortcoming was often lost sight of, indeed Ronald Ross in 1911 still believed that it had not been proved that relapses might occur after the proper administration of quinine At times, dangerously large doses of bark or alkaloid salt were prescribed in an attempt to prevent relapses But the certainty of recurrence in vivax infections after quinine treatment had ample confirmation in every large epidemic, most convincingly during the First World War, and it is a fact no longer seriously disputed

Before leaving the subject of cinchona bark, it is of interest to note an anecdote related by J Rutherfurd Russell

in his *History and Heroes of Medicine*. He recalls that William Cullen, in 1789, published his famous *Materia Medica* in which he stressed the beneficial effects of bark in the treatment of ague. He believed that the bark excited a tonic state of the stomach muscles, this being readily communicated to the rest of the system so that it overcame the loss of muscular tone believed to cause the symptoms of ague. Samuel Hahnemann translated Cullen's work into German and was not fully satisfied with the explanation of the action of bark on ague. Hahnemann was certain that the bark was effective in ague but not that there was in fact a mysterious tonic state of muscles involved. So he decided to experiment on himself by taking a dose of bark to see if he could note any changes produced by it in his body. He took 4 drams in successive doses, being at the time in good health. By chance, a few days after administering this remedy to himself, he developed the first symptoms of ague. This happened in Leipzig where at the time intermittents were common. The dramatic result led Hahnemann to a bold theory that the power of a substance to cure a morbid condition was associated with the power to produce in a healthy person a state resembling that which it had the power to cure; and so arose the idea of Homoeopathy!

The Cinchona Alkaloids

Until the early nineteenth century the crude bark itself was the basis for the powders, infusions, tinctures, and other formulations used in malaria therapy. Many, including Paracelsus, had attempted to isolate the active principle of cinchona but without making any progress until 1745, when Claude Toussaint Marot de Cagarage discovered what he called a *salt deviation* in an alcoholic liquor of cinchona bark. Forty years later, Sigismund Hermbstadt established that this action was due to an alkaline salt to which another observer, Hoffman, some years afterwards gave the name of *quina-acid*. Then in 1810 Bernardino Antonio Gomes of Lisbon isolated a crystalline substance from an alcoholic extract of the bark. He called it *cinchonino* but did not succeed in purifying it. Finally came the funda-

mental and outstanding discovery by Pierre Joseph Pelletier, aged thirty-two, a remarkably gifted pharmacist and son of a pharmacist, and Joseph Bienaimé Caventou, aged twenty-five, another pharmacist, who in 1820 in Paris, isolated two of the four basic cinchona alkaloids—quinine and cinchonine This brilliant pair, incidentally, had isolated chlorophyll in 1817, and strychnine in 1818 For their cinchona achievement they received a prize of 10 000 francs from the Paris Institute of Science but they did not profit to any great extent commercially because purposely they did not take out patents These workers also found that both alkaloids had been present in the *cinchonino* of Gomes The other principal alkaloids of cinchona are quinidine, found in 1833, and cinchonidine, found in 1844

In 1856 William Perkin, aged eighteen, set out to synthesize quinine at the Pullars Dye Works in Perth Along the road he stumbled on mauve purple, the first of the aniline dyes By this fortunate accident Perkin prepared the way for the stupendous coal-tar chemical industry Small wonder that he was deflected from his original goal More than eighty years later, in 1944, two Harvard chemists, each twenty-seven years old, R B Woodward and W E Doering, brilliantly succeeded in a synthesis of quinine Their efforts had been stimulated by the shortage of cinchona products in Allied countries in the early years of the Second World War This synthesis is still too complicated for commercial use, but should the need appear, it could doubtless be simplified

Following the isolation of quinine in 1820, factories were quickly established in various parts of the world An anonymous writer in the *Chemist and Druggist* (1930) stated that Howards & Sons, Ltd , believed that Alexander Low, a medical man, was the first to manufacture quinine sulphate, 'probably in 1820, at St Aubin, Jersey' He is said to have sold some through his brother in Calcutta But other writers credit Pelletier with the first commercial manufacture Howards began to make it in 1827

England states that by 1823 the manufacture of quinine sulphate was fairly well established in Philadelphia Grier

gives the date as 1822, soon after the discovery of the alkaloid The first selling price was at the rate of $16 per ounce or more than $24 per ounce for smaller amounts Prices per ounce had fallen to less than $2 in 1834, rose to almost $4 in 1864, were occasionally as high as $15 during the Civil War and then declined to less than 50 cents by 1890 According to Farr, between 1868 and 1897, inclusive, almost 100 million pounds of cinchona bark and nearly 16 million ounces of quinine sulphate were imported into the United States During the Civil War, according to Churchman, the Union Army used over 19 tons of quinine sulphate and over 9½ tons of sulphate of cinchona

Grier states that the cinchona alkaloids were first used in place of bark for the treatment of intermittent fever by 'Homel' in 1821 No doubt the man in mind was the French physician A F Chomel who in *Des fievres et des maladies pestilentielles*, published in Paris in 1821, described successful clinical trials with samples of quinine sulphate and of cinchonine supplied by M Pelletier The alkaloid first appeared in the London Pharmacopoeia in 1836, along with morphine and strychnine

One might summarize the state of malaria therapy at the close of the nineteenth century by presenting the divisions in the cataloguing of the treatment of malarial fevers as used in the Index-catalogue of the Surgeon General's Library in 1883 After the first general category 'Treatment of malarial fevers' comes a series of subheadings, 'Treatment of malarial fevers by ' in which each of the following has place arsenic, blood-letting, carbolic acid, chlorate of sodium, cinchona and its alkaloids, cold baths, electricity, Eucalyptus globulus, iodine, iron and its salts, ligature, mercurials, Nux vomica and strychnine, quinine—endermic and hypodermic methods, Salix, salicin and salicylates, spider's web In volume v, second series, 1900, additional headings were alum, animal extracts and serumtherapy, methylene blue, mineral waters, pereirine, and phenocoll Since numerous articles, even books, are included in each category, it is obvious that cinchona and its alkaloids, although certainly predominant, did not have the field to themselves

7

THE MODERN PERIOD

Pamaquine and Mepacrine

By the time of the Second World War, there was well nigh universal acceptance of Manson's dictum that it was culpable trifling to use any drug to the exclusion of quinine when treating acute malaria Many nostrums, of course, made an appeal, some winning temporary or local favour but only quinine stayed the course The supply of the alkaloid salts, although by no means sufficient for total needs, was usually not far behind the demand and, thanks to Dutch efficiency, the price had fallen notably But during the First World War German authorities became apprehensive lest their supplies from the Netherlands Indies be cut off In the East African campaign their forces had been deprived of quinine in highly malarious areas and this distressing experience, with the fear that it might become more general, led to a strong desire for a synthetic antimalarial of German manufacture So, the I G Farben Industrie at Elberfeld was requested to undertake the preparation of such a drug to replace the natural alkaloid

Interestingly, the starting point chosen for this attempt to manufacture an antimalarial was not quinine but methylene blue For in 1891, with the assistance of Professor Guttmann, a clinician, Paul Ehrlich, having studied the biological uses of methylene blue for some fourteen years, had administered it to a patient with malaria and had seemingly produced therapeutic benefit This trial, incidentally, appears to have been the first in which a medicinal drug of any sort, natural or synthetic, was appraised for curative powers derived from direct action on an infecting organism In other words, it was the first 'chemotherapy' as the word was used by Ehrlich With this story in mind, Schulemann, Schonhofer, and Wingler set out to enhance the anti malarial properties of methylene blue by adding to or

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changing the architectural design of its molecules Cleverly, their colleague Roehl assisted by testing the resulting numerous experimental products in canaries infected with avian malaria It was assumed that a compound that destroyed or inhibited the plasmodia in birds might act similarly against those infecting man and that the bird trials might give some clue to the toxicity of the new drugs For, or course, it is the aim of chemotherapy to destroy the parasite, not the patient

This efficient team of investigators after some years of painstaking study came up with *plasmochin*, as reported by Roehl and by Horlein in 1926 and by Schulemann and colleagues in 1927 and 1932 Here was a most important advance, not because plasmochin itself ever became very useful but because of the fresh and original approach Indeed it marked the beginning of a new period in malaria chemotherapy

Plasmochin, known in the United Kingdom as *pamaquine*, had three properties not possessed by quinine it rendered falciparum gametocytes or crescents non-infectious to mosquitoes, it could prevent malaria infection when administered during the period immediately after sporozoite inoculation, and, when combined with quinine, it tended to prevent vivax relapses But it was a very toxic drug and caused several fatalities during its early use so that it was obviously not practical

The Elberfeld laboratory project prepared and tested no fewer than 12,000 compounds among which another and more useful anti-malarial was found, soon after plasmochin This second product was called *atebrin*, now known in Britain as *mepacrine* and in America as *quinacrine* Schulemann first reported it in 1932 It had been synthesized by Mauss and Mietszch, as published in 1933 The bird testing had been done by Kikuth, whose report appeared in 1932

Mepacrine is a yellow dye and it will temporarily tint the skin of persons who take it regularly It has, however, proved to be a useful substitute for quinine, having much the same limiting effect on the various species and stages of malaria parasites It has one great advantage in that the

human body does not excrete it rapidly Quinine is quickly eliminated but mepacrine persists in quantities effective against malaria parasites for at least a week after the last dose This quality has greatly added to its value as a prophylactic Mepacrine also delays malaria relapses for longer periods than does quinine

Prior to the Second World War the Germans had gone one or two steps farther in their studies and had synthesized *resochin*, now known as *chloroquine*, which, strangely enough, they discarded as too toxic after a superficial study A similar drug, called *sontochin*, was being tested in a limited way by Germans and more extensively by the French The latter used the drug in North Africa where it was found by Allied Forces and sent to the United States for study This led to the independent synthesis of chloroquine and *amodiaquin* and to the discovery of their usefulness as antimalarials

Chloroquine is now manufactured in America as *aralen* and in France and Britain as *nivaquine* A related and almost equally effective compound is amodiaquin or *camoquin*, manufactured in the United States These drugs are less toxic than mepacrine and do not stain the skin Extensive investigations have demonstrated that chloroquine and camoquin, although not completely satisfactory in that neither one will with certainty prevent vivax relapses, are excellent antimalarials for therapy or prophylaxis

Period of the Second World War

Ninety per cent of the world's usual sources of quinine were denied to the Allies when the Japanese occupied Indonesia To be sure, there were plantations of cinchona in India and there were still some trees in South America, but both areas had been importing bark and alkaloids from Java to meet their own needs Since it is axiomatic that, in the absence of an effective anti-malarial drug, troops cannot operate successfully where malaria is highly endemic, the loss of Java's cinchona created a real problem because Allied troops were heavily committed in some of the most malarious areas of the world

Several effective moves were made at once to meet the emergency. First, the War Production Board in the United States issued Quinine Order M-131. This made inaccessible to commerce all existing stocks of quinine and restricted the use of all cinchona alkaloids almost completely to the treatment of malaria. The same Board made persuasive appeals to owners of alkaloid supplies to send these to the Board, which analysed them and pooled by type all receipts. By these means, surprisingly large stocks of quinine and other cinchona alkaloids were built up in reserve by the Board for possible military needs.

The National Research Council co-operated by investigating and then recommending the use of *totaquine* as a substitute for quinine. Totaquine is a standardized preparation of the total alkaloids of cinchona bark, suggested by the Malaria Commission of the Health Organization of the League of Nations in 1931. This preparation can be made from barks inferior in quinine content but sufficiently rich in other crystallizable alkaloids. It will combat malaria almost as effectively as quinine alone, since each of the four principal cinchona alkaloids has essentially the same over-all anti-malarial effect.

Another important move by the War Production Board was the stimulation of the manufacture of mepacrine. It was first necessary that chemists work out the synthesis of certain intermediate constituents which the Germans had not permitted to be manufactured abroad. Then, greatly enlarged factory facilities were required. But these hurdles were surmounted so successfully that there was never a shortage of mepacrine among the Military Forces due to insufficient production. Concurrently, the National Research Council sponsored extensive chemical, pharmacologic, and clinical investigations of mepacrine which soon made it possible to recommend intensive use of this drug with confidence. In all of these measures, there was the fullest co-operation between the Allied governments, particularly between Australia, the United Kingdom, and the United States.

Among the immediate steps taken by the Board of

Economic Warfare was a move to increase the importation of cinchona bark from South America Cinchona agreements were made with several Andean republics that together had once produced the world's supply The agreements consisted essentially of a guarantee to buy all the suitable bark that could be shipped, and of offers to provide technical aid to bark harvesters, dealers, and plantations

Attempts were made to start new cinchona plantings from seeds which had been taken out of Mindanao in April 1942 by Colonel A F Fischer, who for years had been director of the Philippine Bureau of Forestry Not many realized that in Bukidnon, Mindanao, there was a small but thriving cinchona plantation which, at the time the Second World War started, was producing 600 to 1,000 pounds of bark daily In March of 1942 Colonel Fischer was seriously ill on Bataan with dysentery and malaria One day when he asked for quinine he was told that supplies were nearly exhausted As soon as he could move he persuaded General Wainwright to let him fly the gauntlet to Mindanao to attempt to produce supplies of cinchona In Bukidnon, machinery was improvised, bark gathered and pulverized Although it proved impossible to get it back to Bataan, it was this bark, more than any other single material factor, that helped to maintain the long and tenacious resistance of guerrilla forces against the Japanese, who did not garrison the area for some time after the fall of Corregidor Father Haggerty, S J, who was associated with the Bukidnon bark production during the emergency, wrote to Judge Patterson, the Under-Secretary of War, that during the occupation 'we were able to ship cinchona bark throughout Mindanao and the Southern Philippines, using this bark in its crude form for the prevention of malaria and for its cure I estimate that tens of thousands of lives were saved by it' Here was a modern 'Jesuit's bark' which lived up to the high traditions of the original, distributed three centuries earlier

Under special orders, Colonel Fischer was sent out of Mindanao to Australia His only luggage in the overcrowded plane was a milk can full of cinchona seeds consisting of some thirty-nine selections resulting from previous

Fig 11 *Cinchona succirubra* Pav.

Courtesy of the Wellcome Historical Medical Museum From a photograph presented by Professor A. Tschirch

effort to build up quinine supplies, to stimulate the use of totaquine, and to develop new sources of bark was most noteworthy and at the time it seemed vital

What developed into the most important step in the United States stimulated by the quinine crisis, was the organization of an extensive programme of research in the chemotherapy of malaria This involved the work of a large group of university and industrial scientists, sponsored and supported by the Committee on Medical Research of the Office of Scientific Research and Development The latter was a part of the Office of Emergency Management created by President Roosevelt by Executive Order on 28 June 1941 This programme involved close co operation by scientific institutions, pharmaceutical firms, private individuals, the United States Army, Navy, and Public Health Service, and a most effective liaison with United Kingdom and Australian authorities The programme was well co-ordinated, at first by a series of sub committees and conferences, and, from November 1943 onwards, by the Board for the Co ordination of Malaria Studies, with the helping hand and facilities of the National Research Council

The chemotherapeutic studies involved the preliminary screening of over 14,000 compounds for various types of anti malarial activities in several avian infections, an analysis of the toxicology and pharmacology of many of these compounds in laboratory animals, and an investigation of the potentialities of about eighty compounds in human malaria The net result of these studies, in which some thirty-five university or college laboratories as well as numerous other facilities were utilized, was the discovery of anti-malaria activity in compounds derived from a variety of structural types There was also evolved a much clearer definition of the problems underlying the suppression and cure of malaria The following practical advances may be attributed to this co operative war-time programme

1 The development of reliable methods for the quantitative appraisal of anti-malarial activity

2 The development of better methods for the use of mepacrine in the suppression and treatment of malaria

These were based largely on the studies of Shannon and colleagues, of the Research Service, Goldwater Memorial Hospital, New York They developed quantitative measures of mepacrine blood-plasma levels They also demonstrated that mepacrine, contrary to quinine, is extensively localized in many of the body tissues and is degraded at a low rate Larger initial 'priming' doses caused prompt termination of clinical activity in malaria, a result not the rule with evenly spaced dosage of this drug Daily, instead of weekly, prophylactic doses maintained effectively suppressive plasma levels not previously seen consistently in practice These results led to the demonstration that mepacrine was superior to quinine in some respects Here was a long step towards depriving the Japanese of any advantage their possession of the major sources of cinchona might have had

3 The development of compounds better than mepacrine One of these already mentioned was the resochin, now called chloroquine, which the Germans had synthesized before the war but which neither they nor others had evaluated properly until after its development in the United States in 1944 Chloroquine is more rapid in action than mepacrine, and it can be administered in very short therapeutic courses, even in a single dose if necessary Taken only once a week it provides effective suppression, preventing acute attacks even under highly endemic conditions Finally, it is less apt to cause gastro-intestinal distress and it does not tint the skin A variant of chloroquine, and almost equally effective, is amodiaquin or camoquin, mentioned above These two drugs at the moment share highest honours in malaria therapy

4 The programme also included a study of pamaquine, which, as early as 1930, had been shown to be useful in combination with quinine to stop the relapses of vivax malaria, not prevented by quinine, mepacrine, or chloroquine The difficulty with pamaquine, as already mentioned, is its toxicity The effective dose is also a poisonous dose to some individuals This fact led to the development of three compounds, called *pentaquine*, *isopentaquine*, and finally *primaquine* All have the pamaquine effect on vivax malaria

and are less toxic The best of the three is primaquine, synthesized by Professor Robert Elderfield at Columbia University It has been used extensively to cure relapsing vivax malaria in soldiers returning from Korea

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In the United Kingdom, not only was there intense study of mepacrine and close affiliation with the programme of investigation in the United States, but there was also an independent search for new compounds Under the aegis of Imperial Chemical Industries, Ltd , and with the priceless assistance of the late Professor Warrington Yorke of the Liverpool School of Tropical Medicine, hundreds of compounds were tested for anti-malarial activity, particularly for the power to destroy or inhibit the exoerythrocytic forms of the parasite It was a long search, but finally, in November 1944, it resulted in *paludrine*, the 4,888th compound tested in the project Paludrine, now called *proguanil* in the United Kingdom and *chlorguanide* in the United States, was reported by Curd, Davey, and Rose in 1945, with clinical tests also reported in 1945 by Adams and Maegraith of the Liverpool School of Tropical Medicine, and by others It has a chemical structure quite different from that of quinine, mepacrine, and chloroquine Proguanil has a wide margin of safety in usage and it is an inexpensive drug It exerts therapeutic and suppressive action against all forms of malaria and it has the unique quality of attacking or inhibiting the pre-erythrocytic stage of *P falciparum* But it has wide variation in effectiveness against the several strains of falciparum plasmodia, it is relatively slow-acting, and it induces the development of resistant strains, so its place in malaria therapy is not certain

Finally, by Anglo-American combined operation, the most recent anti-malarial drug, *pyrimethamine*, called *daraprim*, has been developed It, like proguanil, represents progress in development of a new type of compound The chemical structure of pyrimethamine resembles that of a proguanil metabolite Its anti-malaria properties were noted

by a group of biochemists under the leadership of George Hitchings in the Burroughs-Wellcome Research Laboratories in 1949 in Tuckahoe, New York. Pyrimethamine is cheap, colourless, and tasteless, and it costs about one-fourth as much as chloroquine per treatment or course of prophylaxis. This new drug has slow therapeutic action but it has strong prophylactic properties. However, it is still too young a product to have demonstrated its qualities beyond question.

All in all, the Japanese invasion of Indonesia resulted in a ten-year programme of intensive investigation of antimalarials that, in scope and results, is unequalled in the history of chemotherapy.

Volunteers

One phase of the ten-year intensive search for better drugs for malaria therapy deserves special mention. Along with laboratory studies there were clinical experiments on humans on a scale never before attempted and perhaps impossible except under the urgency of war. Only those projects involving the infecting of volunteers with malaria will be described. There were numerous others in which volunteers were used to test the toxicity of anti-malarials and to measure drug concentration levels in the blood. For example, much fundamental work of this sort with mepacrine in men and women volunteers was done by Maegraith and colleagues of the British Army Malaria Research Unit co-operating with the Nuffield Institute for Medical Research in Oxford. There were also trials of prophylactics in groups of Allied soldiers purposely exposed to malaria under field conditions.

During 1942 and the first half of 1943, malaria casualties in combat zones among the Allied troops in the South West Pacific, as elsewhere, far exceeded battle casualties, in ratios sometimes as high as 30 to 1. Malaria created two outstanding man-power problems, first an excessive number of primary cases in a war of movement in highly endemic areas, and secondly, a very high rate of relapsing vivax malaria in troops who had returned to base areas. The

situation was undoubtedly critical General MacArthur remarked to me at the time that it would be a very long war indeed if for every division facing the Japanese he must count on a second division in hospital with acute malaria, and a third division in a convalescent depot with relapsing malaria

To attempt to solve these urgent problems there was set up in June 1943, with the authority of General MacArthur and on the advice of the D G M S , Australia, a Land Headquarters Medical Research Unit in Cairns, under Sir Neil, then Brigadier Hamilton Fairley The directive to this Unit was that it should investigate the mode of action and precise value of available anti-malarial drugs as suppressants and true prophylactics in volunteers deliberately infected with Papuan strains of *P vivax* and *P falciparum* A second Research Group continued the studies through a prolonged convalescent stage at another medical centre

The full story of the magnificent work of Fairley's L H Q Medical Research Unit in Australia cannot be told in a brief lecture, but it is a classic in the annals of medical history As the late Colonel James said, it marked an epoch in malaria research High tribute is due to the Australian soldiers who so willingly volunteered, risking health and even life for the welfare of their comrades in arms and for the benefit of science

One of the first and most important results of these experiments became evident at a Military Conference on the Prevention of Disease in Tropical Warfare, held at Atherton in Northern Queensland in June 1944 Here there was official acceptance of the fact, demonstrated by Fairley's group, that if soldiers actually took a tablet of mepacrine each day it would be possible for them to fight for many months in hyperendemic malaria areas without significant malaria casualties There would be no deaths from malaria, no blackwater fever, and no soldiers infectious to mosquitoes within the force Only after stopping the suppressive mepacrine would there be a residual problem of relapsing vivax malaria

When these facts were made the basis of actual practice, there was a phenomenal drop in malaria casualties For

example, the malaria hospital admission rate among the troops in New Guinea in December 1943 was 740 per 1,000 per annum, but in November 1944 this rate had fallen to 26 per 1,000 per annum With the single exception of one area in which there was a strain of *P falciparum* unusually insusceptible to mepacrine, the results of the Cairns experiments were confirmed on a vast scale not only in the South West Pacific but in other theatres of war

Later, the Cairns group investigated proguanil in a similar way and demonstrated on human volunteers its usefulness as an anti-malarial drug Incidentally, it was shown that the mepacrine-insusceptible strain, previously mentioned, was fully amenable to proguanil

Altogether nearly a thousand volunteers from the Australian Army were used in the malaria experiments, which added still more lustre to the notable history of these forces in the Second World War

In the United States the testing of anti-malarials in mentally diseased patients who were undergoing treatment by being subjected to malarial fevers was the method employed at first It will be recalled that Yorke and Macfie of the Liverpool School of Tropical Medicine were the first systematically to infect general paretics with malaria by means of mosquitoes, so that they could study the disease as a natural mosquito-borne infection James and Shute at the Horton Mental Hospital developed techniques for transmission, treatment, and observation which were early models for such experimentation throughout the world Prior to 1942, Boyd and his colleagues in Tallahassee and several other observers developed useful methods and carried out numerous study projects, using paretics The testing of anti-malaria drugs in paretics during the war period was begun by Coatney and Cooper at the National Institutes of Health in May 1942, and during the next year and a half some 125 patients were used Incidentally, Warrington Yorke visited this project in 1942 and was much interested in some of the techniques, such as the use of one infected mosquito to bite and to infect three patients in immediate succession

But the use of paretics provided quite inadequate facilities for the expanded war-time programme of investigation of old and new malaria drugs. So arrangements were made to use volunteers in a number of prisons. For example, Coatney and his group at the National Institutes of Health of the United States Public Health Service, organized studies at the Federal Penitentiary in Atlanta, with strong support from the Bureau of Prisons. This was a prototype for later projects. Here, between March 1944 and November 1946, 136 volunteers were infected with malaria by mosquitoes and another ten by blood inoculations. No fewer than 287 separate attacks of malaria were meticulously studied, especially as regards the relapse characteristics of two strains of *Plasmodium vivax*. Subjects were carefully selected on the basis of health and previous freedom from malaria. For this selection there was a long list of volunteers who, as a contribution to the national war effort, were enthusiastically willing to risk the discomforts and uncertainties both of malaria and of experimental drugs. The volunteers who became infected were given money bonuses and certificates of merit but, at first, no remittance of sentences. In a second Atlanta series, 'meritorious good time' equal to five days a month was deducted.

From 1946 to 1950 the same group of investigators carried out a similar project in the Federal Correctional Institution in Seagoville, Texas, where 273 volunteers were used. In this work a money bonus was given to each infected volunteer and a 'day for day' or greater remittance of sentence by the Army, sometimes up to as much as three years. Many of the Seagoville volunteers donated their bonuses to the Red Cross or to a Crippled Children's Fund, or sent them home to their families.

In 1951–3 a further series of experiments in 422 volunteers indicated the value of primaquine in the treatment of vivax malaria and of daraprim in suppression. These studies were supplemented in 1952 at Forts Benning and Knox, where several hundred soldiers volunteered for primaquine tests which established the fact that primaquine is safe and effective for the radical cure of vivax malaria. No other

anti-malarial is so useful in the prevention of the relapses characteristic of vivax malaria

Another group of observers, under Doctor Alf S Alving of the University of Chicago, and with the co-operation of the Army Medical Corps, made similar studies at the Illinois State Penitentiary from 1944 until 1947 and from January 1950 to date More than 625 prisoners have volunteered for these experiments Each, if infected with malaria, was paid a sum of money which could be spent in the prison commissary Each also received a Certificate of Merit, signed by the Surgeon General of the United States Public Health Service and, in later experiments, by the Surgeon General of the Army

One must emphasize that these prisoner subjects of experimental malaria were in all cases genuine volunteers and that there was always a long waiting-list of applicants, most of whom were sincere in their desire either to be of some service to their country in winning the war or to have a part in the search for much-needed medicines Some of the prisoners were reacting to the first worthy impulse experienced in many years There was one young man whom I met who was under a long sentence and whose history was that of chronic incorrigibility Indeed, his family had disowned him and his father had vowed never again to communicate with him This prisoner volunteered, experienced a long bout of malaria, and was given a certificate of merit He sent this document to his father, who thereupon wrote back saying, 'My son, for the first time since you were a small boy I am proud of you'

As regards malaria studies, the *esprit de corps* of the band of embezzlers, rapists, and murderers in the Illinois Penitentiary, who risked their health to make possible the testing of anti-malarial drugs, was truly amazing Having seen it, one denies and greatly deprecates any suggestion that their volunteering was due to official pressure

It is axiomatic that new knowledge in therapeutics is established by systematic trial and error, in other words, by experimentation Test-tubes have had great usefulness and animals have been absolutely indispensable to supplement

the *in vitro* studies, indeed, many of the most useful advances in medicine would have been utterly impossible without the use of laboratory animals But, however clear the results in test-tubes and living animals, there must come the crucial trials in man himself No matter how complete the preliminary screening of a drug, there may remain not only some doubt as to its effectiveness but also some risk of its being toxic in man The fact often makes it necessary to call for volunteers for final testing of a new remedy

Medical history abounds in stories, some highly dramatic, of laymen, laboratory workers, and physicians who have willingly offered themselves for such trail-blazing experiments Sometimes, as in the war-period study of anti-malaria drugs, subjects in fairly large numbers have been required and there has been an appeal to groups of students or of prisoners or of soldiers One realizes the special dangers inherent in the use of prisoner or soldier volunteers whose human rights may perhaps be easily infringed Once such rights are denied to the subjects, an experiment may involve sheer brutality But the Allied war-time use of human volunteers described above has had the traditional heroic and classic flavour Volunteers were always told the actual truth as regards the nature of expected illness, probable results, and possible dangers Careful scrutiny of the records, and some personal acquaintance of the projects, have aroused nothing but the utmost respect for the intelligent and humane approach of the experimenters and for the courage and devotion of the volunteers All honour to them!

Out of the various projects of this kind came much practical documentation of the curative and therapeutic action of quinine, mepacrine, and pamaquine With this background it has also been possible to evaluate over thirty new anti-malarial compounds, including the promising chloroquin, camoquin, proguanil, isopentaquine, primaquine, and daraprim

Drug Resistance

Ehrlich, almost fifty years ago, noticed that trypanosome parasites in man's blood might become resistant to drugs that

at first killed them It is now well known that some microscopic organisms and some noxious insects can change their metabolism so that they are insusceptible to certain poisons In time, a strong tolerance or resistance is developed This phenomenon is now being encountered in malaria parasites, unexpectedly, because during more than 300 years of exposure they never succeeded in developing significant resistance to cinchona or its alkaloids To be sure, some strains of certain species of plasmodia have apparently always been more susceptible than others to quinine For example, Roman and Sardinian strains of *P falciparum* require something like eight times the dose that will successfully subdue Indian strains of the same species This relative resistance seems to be inherent and not a developed response to drug therapy. But in the case of some newer synthetic antimalarials, such as proguanil, there has appeared a problem of drug-resistance aroused by repeated administration of doses less than lethal to the parasites

In 1947 Ann Bishop and Betty Birkett, of the Molteno Institute, University of Cambridge, and, independently, Williamson, Bertram, and Lourie, found a forty-fold increase in resistance to proguanil in the case of *P gallinaceum*, a species of avian malaria Moreover, they proved that the *resistant strain retained its tolerance even after it had* been transmitted to new avian hosts by mosquitoes The same tendency in respect of proguanil was then observed by several in the case of *P cynomolgi* of monkey malaria Finally, in 1949, plasmodia of humans—*falciparum* and *vivax*—were shown to have this same disconcerting ability to develop a *resistance to proguanil and this is likewise* undiminished by mosquito passage to new hosts In one series of observations there was a thousand-fold increase in resistance developed by *P vivax* against proguanil

This, obviously, is a serious matter, because once a resistant strain has been developed in an area it will persist and mosquitoes will disseminate it widely, even to the point where the drug would have little value in the entire locality There have already been reports that such a spreading of proguanil-resistant *P falciparum, vivax* and *malariae* is

actually taking place—the first-named in Malaya and the last two in Indonesia One important fact that has come out of experimental studies is that such resistance to proguanil does not develop if ample dosage is employed from the outset of therapy or suppressive treatment—in other words, if the drug is administered in amounts sufficient to overwhelm the parasite before it can develop a tolerance

There are cases of cross-resistance as, for instance, the development of proguanil-tolerance while *P gallinaceum* is becoming resistant to sulphadiazine Fortunately, this phenomenon is not common Proguanil-resistant strains remain normally sensitive to quinine, chloroquine, mepacrine, and pentaquine Recently it has been shown by Rollo that resistance to daraprim can be developed by *P gallinaceum* and *P berghei* Attempts to produce resistance to mepacrine, chloroquine, pentaquine, and isopentaquine have not succeeded and, in the case of quinine only a two fold increase in resistance has been obtained More recently, pyrimethamine has been shown to develop resistance in *P cynomolgi*

Much remains to be done in the evaluation of the newer synthetic anti-malarials and we are still searching for that *therapia sterilisans magna* that has for so long been man's goal Great progress has been made and we have attempted to describe some of the incidents and scenery along the road Certainly, from early days to the present time, man's therapeutic efforts against malaria have indeed constituted a tangled skein that is not yet fully unravelled But, thanks to the efforts of many scientists in many lands, the pattern has begun to assume a much more useful and orderly form Having started with herbs and charms and spiders, and after more than 300 years of cinchona bark and quinine we now have for malaria therapy some of the most effective specifics in the entire pharmacopoeia At last we have an impregnable second line of defence against the disease that has for centuries menaced a large proportion of the world's population

SECTION III

THE DEVELOPMENT OF MALARIA PROPHYLAXIS

THE story of the development of malaria prophylaxis merits the pen of a master historian Antiquity of backgrounds, drama of episodes, brilliance of personalities, immense social connotations of failures and successes, provide substantial and ornate materials for a superb narrative But this cannot be a definitive history Instead, here is an attempt to whet appetites, to illuminate for retrospect a few of the many facets, to provide what might be called an introduction to the annals of man's attempt to protect himself from the intermittent fevers

I fully agree with the editor of *The Lancet* who, referring to the 1952 Heath Clark lectures, wrote that history is a necessary instrument of policy, an important discipline in medical teaching So I hope that profit will derive from this attempt to lift out of the envelope of the past, certain events and careers that have contributed to the immense expansion of malaria control It is an amazing tale Who could have foreseen at any time prior to the last decade that the personal act of hand-slapping a mosquito would develop into community spray-killing methods that have effected almost total expulsion of malaria from entire countries?

Malaria prophylaxis as it now flourishes has four principal roots drainage, drugs, larvicides, and adulticides, each of which I propose to discuss briefly

8

DRAINAGE

APOLLO the Sun God killing the Delphic python, Hercules slaying the Lernaean hydra, clearing away the pestiferous filth of the Augean stables, destroying the obscene Lake Stymphalian birds, all have been said to symbolize man's struggle against paludism, his attempts to bonify disease-causing swamps

Another legend obscured by the mists of mythology is that of Empedocles of Agrigentum, Sicily (*fl* fifth century B C), pupil of Pythagoras, poet, philosopher, physicist, physician, social reformer, and legendary hero Galen referred to him as the founder of Italian School of Medicine and Aristotle called him 'inventor of rhetoric' Much mystery shrouds his life and death, but one episode, apocryphal though it may be, has especial interest Diogenes Laertius (viii 70–71) referred to it as follows

> We are told that the people of Selinus suffered from pestilence owing to the noisome smells from the river hard by, so that the citizens themselves perished and their women died in childbirth that Empedocles conceived the plan of bringing two neighbouring rivers to the place at his own expense, and that by this admixture he sweetened the waters When in this way the pestilence had been stayed and the Selinuntines were feasting on the river bank Empedocles appeared, and the company rose up and worshipped and prayed to him as to a god It was then to confirm this belief of theirs that he lept into the fire These stories are contradicted by Timaeus, who expressly says that he left Sicily for Peloponnesus and never returned at all (*Translation by Hicks*)

The situation confronting Empedocles may have been similar to that sometimes encountered by malariologists in modern times The 'noisome smells' may have arisen from the stagnating lower reaches of a river whose outlet had been closed by sand In that case the water would have turned brackish and in Sicily would have favoured the

breeding of a notorious malaria-carrying mosquito—*A sacharovi*, and could have resulted in an epidemic The additional flow of two streams properly utilized would have freshened the water and might even have opened the blocked outfall bringing about reduced breeding of the mosquito vector and thus quieting the epidemic It may have been in this way that Empedocles, in the words of Matthew Arnold, was able to 'cleanse to sweet airs the breath of poisonous streams'

It's a good story, but whether Empedocles was dealing with malaria is questionable But we do know beyond doubt that many Greek and Roman writers clearly associated malaria with marshes, and that some preventive measures were taken on this basis Certainly, ancient Romans led the world of their time in hydraulic engineering skill derived not only from Greek sources but also from the Etruscans The latter were faced with *tufo terroso*, a stratum of impermeable rock underlying certain top-soils of the Roman Campagna The name suggests something formidable that excites terror and it rightly arouses the imagination For, in many places, this compact under-layer blocked the natural drainage essential to soil fertility Moreover, the intense malariousness of the Campagna over centuries has been in large measure traceable to the effects of *tufo terroso* Its impermeability has made inevitable the pools and marshes that provide suitable breeding places for local malaria-carrying mosquitoes

Etruscans of the pre-Roman period must have found *tufo terroso* a serious handicap to farming the area But with surprising ingenuity and engineering skill they constructed an extensive system of underground drainage which conducted water in tunnels through the semi-permeable layer immediately above the *tufo terroso* Many of these Etruscan *cuniculi* are well preserved, in fact a considerable number still function Sometimes called anti-malaria drains, they were probably built, as Celli notes, to provide flowing water for drinking and irrigation purposes and for draining farm land The evidence is inconclusive, but probably so dense, so highly skilled, and so prosperous a rural population as

the Etruscan could not have been very malarious In any case, the *cuniculi* did not greatly reduce the larger marshes and would have had little effect on severe malaria

Many references can be cited to prove that in Roman times marshes were suspect and that drainage as a health measure was suggested For example, as previously noted, Vitruvius (approx 88–26 B C), military engineer to Augustus, wrote that it is better to select a hill site for a house, 'away from marshes, the poisonous exhalations of which exert a morbid influence on man' He mentioned the marsh fogs and mists charged with the 'exhalations of fenny animals' and diffusing 'unwholesome effluvia' over the bodies of nearby inhabitants He further remarked that, 'when the marshes are stagnant and have no drainage, they become putrid and emit vapours of a heavy and pestilential nature'

The Romans accomplished much drainage For instance, the construction of the Cloaca Maxima in Rome was begun by Tarquinius Priscius (616–578 B C) primarily as an underground drain to lower ground-water levels Later it came into use for removal of storm water and sewage The Romans also extended the sub-soil network of the Etruscans and added open drains, some of which effectively dried out a number of marshy areas This work, although chiefly agricultural in purpose, was partly motivated by the fear of swamp-generated disease There was probably fairly wide agreement with Varro's comment 'For though healthy conditions depending as they do upon soil and climate, are not in our power but in Nature's, yet by care we can do much to mitigate the graver evils '

In fact, drainage, for combined agricultural and health improvement, was carried out in Italy intermittently from the days of the Caesars to those of Mussolini During the early Middle Ages, according to Celli, many hydraulic improvements were made or attempted For example, the Patrician Decius tried to drain the Pontine Marshes He was to receive, tax-free, any land he could make arable by drainage, but he had little success All through the Middle Ages there were similar projects to improve land by taking

off water, and there was an almost rhythmical alternation of success and failure John XV (985–96) for instance, was able by drainage to improve greatly the health of those who lived near the Lake of Porto, but a few years later John XVIII (1003–9) was so disturbed by the fevers of the area that he referred to the lake as a 'cursed little stagnant water' John XIX (1024–32) opened up the clogged drains and soon he was calling the same lake 'Blessed', for it had beauty and usefulness

Callixtus II (1119–24) made a determined attack on the marshes of the coast of the Campagna But he failed to ameliorate the malariousness of the area and finally gave up his project

In 1154, the Roman Senate sponsored extensive drainage works and succeeded in drying a troublesome swamp But by the time of Innocent III (1198–1216) the ditches were blocked with silt and the swamp had reappeared so that the whole neighbourhood and even the lower parts of Rome itself were suffering from intermittent fevers As Hildebert of Tours had written in his Elegy for the Eternal City in 1107

> What thou wert when flourishing
>   is shown by the ruins of what fell
> Long centuries have destroyed the
>   splendour, and the castle
> Of the Caesars and the site of the Divine
>   Gods lie in the swamp

Celli notes that serious attempts to turn the desolate marshland around Rome into drier, agriculturally useful soil were made by Boniface VIII (1294–1302), Sixtus V (1585–90), Urban VIII (1623–44), Alexander VII (1655–7), Innocent XII (1691–1700) and Pius VI (1775–99) For example, Urban VIII employed Dutch engineers to drain the Campagna and the Pontine Marshes Even then the Netherlanders had completed some extensive projects in their own country and had a wide reputation for land reclamation The Romans had taught the Dutch how to protect dry land against periodical flooding by the rivers Rhine and Meuse But the drying of swamps and lakes without natural drain-

[illegible] South America in a London warehouse

excellent plans, initiating work in 1810. By the end of four years, one-quarter of the Pontine Marsh area had been made fit for cultivation. But time ran out and the marshes defeated Napoleon, even as they had turned back bishops, popes, and emperors before him. By 1870 malaria was again a major scourge in the Pontina and the Campagna, in fact once again Rome itself was afflicted.

In 1880 a new drainage project was started in the Maccarese area of the Campagna and this was highly successful in reclaiming farmland and in somewhat lessening the malaria burden. This project remained effective until sabotaged by the German Army in 1943–4. Fortunately, the basic plan and construction withstood the effects of wartime flooding and the scheme is again functioning well.

The Pontine Marshes remained victorious over man until 1930 when a modern Caesar named Mussolini made the latest and most successful attempt to drain and reclaim the area. Not a single permanent household existed in the Pontina at that time despite the long history of bonification projects. But when Mussolini's scheme was completed in 1940, more than 50,000 people were living there, not only in rural farm-houses but in three newly built cities. Some 200,000 acres of farmland had been reclaimed to support them—a truly remarkable achievement.

In addition to the advantages of modern tools, Mussolini's engineers had the intelligent help of public-health physicians who knew not only the cause of malaria and the facts of its mosquito transmission, but who also realized that drainage alone will not control malaria in Italy where the vector insect finds canals and ditches highly suitable breeding places. So larviciding, screening, and the use of antimalarial drugs were skilfully integrated into the bonification scheme. Even so, malaria transmission was not completely stopped but the area did become relatively healthful, at long last.

Much more could be written about drainage in reference to malaria control. The history of the English Fens, for example, is an interesting one. Here was an area of over 680,000 acres, at one time inundated periodically by river waters and storm-tides, a source of malaria-carrying mos-

quitoes and of almost no agricultural usefulness This marshy region is now productive and non-malarial because of drainage works extending over two centuries, as for example the Black Sluice District project from 1633 to 1886 The Public Moneys Drainage Act in 1847 and the Private Moneys Drainage Act in 1849 were great stimulants for this and other projects One might also describe the La Gironde scheme, involving the reclamation of nearly 1,500,000 acres in France, and the Haarlem Lake drainage achievement in Holland in 1839–53 which foreshadowed the more recent and much vaster Zuider Zee bonification So, too, there was a great deal of farm drainage in the Middle West of the United States during the eighteenth and nineteenth centuries, supported by laws, excavating machinery, and drain-tiles factories All of these primarily agricultural drainage works paid anti-malarial dividends

Subsoil drains were used in ancient times, but the first modern clay tile or 'land pipes' seem to have originated in France Such pipes have been found in the Covent Garden at Maubeuge in northern France, dating back to 1620 Tile drains were first used in England on the estates of Sir James Graham in Northumberland in 1810 and the first English drain-tile machine was devised in 1843 In the United States, John Johnston, a Scotsman living in Geneva, New York, was the 'Father of tile-drainage' He used it on his farm in 1835 and by 1851 had put down sixteen miles of it Central Park in New York City was tile-drained in 1858

At the turn of this century there were some extensive anti-malaria drainage projects in many places as widely separated as New York and Sierra Leone, Brazil, and Hong Kong Particularly effective malaria control by subsoil drainage has been accomplished by Watson, Evans, Hunter, Scharff, and their successors in Malaya since 1900

9

MALARIA PREVENTION BY DRUGS

BEFORE starting a review of the development of malaria prophylaxis by drugs, it may be useful to note that there are certain underlying considerations, the significance of which has but slowly become apparent. For example, the primary objective may be to protect either individuals or groups, either immunes or non-immunes, either briefly or for prolonged periods, either in accessible or isolated areas. We now realize that it is wise to choose that prophylactic drug and that method of use best suited to the specific needs.

Also, one now differentiates between what J. W. Field calls sporozoite, schizont, and gametocyte 'blockage', respectively. The word 'blockage' implies either destroying parasites, arresting their development, or slowing their rate of multiplying, depending on drug and dosage. By attacking sporozoites or pre-erythrocytic stages one hopes to prevent infection of red cells entirely: this is true causal prophylaxis and the drug a causal prophylactic. By destroying schizonts one expects to keep the numbers of parasites so low that there will be no clinical symptoms: this is suppressive treatment and the drug a schizontocidal or suppressive drug. One may even succeed in destroying all schizonts of *P. falciparum* in this way so that no clinical attack occurs. But in vivax and quartan malaria relapses are usual when the drug has been withheld for a period. Finally, by blocking gametocytes one hopes to prevent the infecting of mosquitoes: this is gametocyte prophylaxis and the drug is gametocidal.

Who first used cinchona to prevent malaria we do not know and there are not many references to the prophylactic use of the bark itself prior to quinine. An early note was by James Lind who in 1768 wrote, 'For farther protection, a wine glass of an infusion of the bark and orange peel in water, or what will prove more effectual, a tablespoonful

of a strong tincture of the bark, in spirits, diluted occasionally with water, may be taken every morning before breakfast' A similar recommendation is made in a book entitled *Domestic Medicine or a Treatise on the Prevention and Cure of Diseases by Regimen and Simple Medicines* in which William Buchan in 1781 discussed 'Of Intermitting Fevers or Agues' He wrote as follows

> To prevent agues, people must endeavour to avoid their causes These have been already pointed out we shall therefore only add one preventive medicine, which may be of use to such as are obliged to live in low marshy countries, or who are liable to frequent attacks of this disease Take an ounce of the best jesuits bark, Virginian snake root, and orange peel of each half an ounce bruise them all together, and infuse for five or six days in a bottle of brandy, Holland gin, or any good spirit, afterwards pour off the clear liquor, and take a wine glass of it twice or thrice a day

Scott notes that about 1839 when the vessel *North Star* was stationed off the coast of Sierra Leone, the twenty crew members took prophylactic bark in wine but the one officer did not and he was the only victim of malaria Again, in 1844, there was a similar demonstration on the vessel *Hydra* those who took bark and wine were spared, the others became ill

Certainly quinine has long been esteemed as a prophylactic drug Taylor, for instance, has retold the interesting story of Arrow Rock in Missouri in the 1830's There, each day during the season, the church bells were rung to remind the citizens to take their prophylactic quinine, available to them in the form of a new proprietary pill which had gained great renown It seems that Doctor John Sappington, having heard that quinine, a 'sovereign and invaluable boon to humanity', was now being manufactured in Philadelphia, had sent his son to buy some The cost was about sixteen dollars an ounce and the instructions were to buy a few ounces By what turned out in the end to be a profitable mistake, the young Sappington lad bought in pounds rather than ounces, thus contracting a debt which threatened financial ruin to his father The latter, however, found the drug to be as effective as expected so he hastily and secretly

made up a quantity into what he labelled as 'Dr Sappington's Anti-fever Pills' With the help of a squad of pill peddlers and the co-operation of church bell-ringers, and aided by some stimulating professional jealousy, he was soon making handsome profits and becoming famous throughout the highly malarious Mississippi Valley The record seems to indicate that, like Talbor, Sappington was not a great doctor or humanitarian but an opportunist with questionable ethics whose activities nevertheless did result in widening the use of quinine

In 1861 the U S Sanitary Commission published the fourth edition of some rules for preserving the health of soldiers Among these was the following 'It is wise and prudent, when ague and fevers are prevalent, that every man should take a dose of quinine bitters at least once in twenty-four hours This will surely serve as a safeguard against an attack of the disease It has been practiced in Florida and elsewhere with undoubted benefit '

In 1863 a sub-committee of this Sanitary Commission reported that

> Now, it is a well established fact in the experience of American physicians, that the daily use of a small quantity of quinine say from three to six grains in one or more doses by those who are exposed to the danger of malarial poisoning will in most instances prevent an attack of malarial disease, and that it will always render the disease milder, if it should occur It will also prevent the development of malarial cachexia

Incidentally, Metcalf in a Sanitary Commission report of the same year, 1863, had written, 'Of the intimate nature of the "paludal poison", "marsh miasmata", or "malaria", we are in complete ignorance ' He suggested the most plausible hypothesis was that of 'sporules of cryptogamic plants' or 'the infinitesimal ova of infusoria'

Systematic mass quinine prophylaxis goes back to Robert Koch, who was first to emphasize this method following the discovery of mosquito transmission of malaria Koch suggested careful treatment of all patients, especially children, as a measure of malaria control In German colonies, due to Koch's prestige, first place was given to this method For

example, at Stephansort in New Guinea in 1900, malaria was said to have been reduced to a minimum by careful quinine treatment, continued for several months Other experiments were carried out in Franzfontein, German South-West Africa, and in Dar-es-Salaam, in German East Africa Professor Claus Schilling in Ronald Ross's book on the prevention of malaria in 1910, with a bow to Koch, concluded that 'the simplest and cheapest method of malaria control *in German colonies is quininisation*', and he even said that it would exterminate malaria from some badly infested places But in the same article, Schilling then bowed to reality and said that 'in many cases quininisation alone will not suffice to reduce the morbidity to a degree which is desirable in the politico-economic interest', and he stated that whether one used mechanical protection, anti-mosquito measures, or quininization would depend on local conditions So by 1910, after very determined attempts to use this method of drug prophylaxis, it had to be admitted that it was not without serious defects

Another ten-year experiment was that of Clark and Komp in some Panamanian villages from 1929 to 1940 Here not only quinine but also plasmochin and atebrine were used Heavy infections were greatly reduced and the constant prophylactic treatment undoubtedly brought much benefit to the villagers But at the end of ten years the parasite rate was 12 1 per cent, a considerable reduction from the original 46 5 per cent but still representing a good deal of malaria, and clear evidence that drug prophylaxis had not eliminated the disease

Many methods have been devised for distributing prophylactic anti-malarials One of the latest and most ingenious is Pinotti's method of mixing chloroquine with common cooking salt This mixture is being distributed in the Amazonia region of Brazil where the inhabitants of vast under-populated areas have long been malarious They are dependent on government salt As a result of experiments a salt-chloroquine mixture has been devised that provides a sufficient amount of the drug at all times in the blood-plasma of the people so that malaria parasites are destroyed

However, practical experience, together with modern tests have made it clear that (1) no drug yet marketed will, in safe doses, prevent sporozoites from taking root in man and developing at least into the early pre-erythrocytic stages (2) drugs like atebrine, paludrine, chloroquine, and camoquin are very useful for individual prophylaxis or to protect groups of persons who must spend weeks or months in malarious places (3) malaria cannot yet be eradicated from an average community by the distribution of drugs (4) under all but highly exceptional circumstances, community malaria control by anti-mosquito measures is cheaper and more effective than by the use of drugs

No spectacular drug wand exists for the control of malaria True enough, *if* in a community every case of malaria, acute and chronic, could be simultaneously treated to complete cure, and if concurrently every mosquito that was carrying malaria parasites within its body could be destroyed or purged of its parasites, then indeed no further transmission of malaria would occur—until parasites were introduced from outside the cleansed area, by man or mosquito However, the difficulties of mass therapy are enormous Absentees, objecting individualists, mothers refusing to have infants and toddlers treated—these are always problems no matter how freely or thoroughly mass treatment is given The cost of trained personnel essential to administer mass therapy is usually higher than the cost of residual spraying

Personal prophylaxis and the protection of troops and labourers from malaria have now reached a high degree of perfection with the newer drugs such as mepacrine, chloroquine, amodiaquin, proguanil, and pyrimethamine Moreover, widespread use of the newer anti malarials will certainly reduce severe clinical malaria in a community to a low point The fullest practical use of anti-malarial drugs should always be included in a malaria-control scheme But, so far, malaria has never been eliminated from a community by drug prophylaxis, nor has the incidence of the disease been reduced by mass therapy so rapidly, so thoroughly, or so permanently as it has been by larviciding, and especially by residual spraying

10

LARVICIDES

THAT method of combating malaria, as well as dengue and yellow fever, that gave greatest promise of success at the beginning of the century was the prevention of mosquito breeding by anti-larval measures, especially by the use of larvicides. Techniques began to be perfected after Ross and the Italians and Reed, respectively, reported their fundamental discoveries proving that malaria and yellow fever are transmitted by mosquitoes. Indeed Ross himself, in 1899, in Sierra Leone carried out the first significant anti-malarial work based on his own discovery. It is notable that Ross later wrote: 'My work had been done not at all for the sake of parasitology, but in order to find a method for reducing the incidence of malaria amongst the inhabitants of warm countries.' His prime interest to the end of his days was malaria control.

The records do not tell us when oils were first used to destroy mosquito larvae. Strabo related that in the time of Nebuchadrezzar, some 600 years before Christ, naphtha or liquid asphalt was taken from the soil of Mesopotamia. Did some observer in ancient days notice that this substance killed certain aquatic forms of insect life? This seems likely. But the earliest record of the use of oils against mosquito larvae that has come to my attention is a note in Dunlap's *American Daily Advertiser*, Philadelphia, in 1793. This states that 'common oil' (whale oil?) would kill mosquitoes breeding in rain-water casks or in cisterns. Delboeuf, in 1895, said that he had used oil as a remedy against mosquitoes for fifty years. He referred to an article in the *Magasin Pittoresque* of 1847 which described the use of oil to kill mosquito larvae as a long-known procedure.

The first well in the United States for petroleum oil was drilled in 1859 in Pennsylvania. The outstanding American entomologist, L. O. Howard, in 1867, observed how this

'illuminating oil' killed aquatic stages of mosquitoes when he accidentally spilled some in a watering-trough. Howard also performed some pioneer experiments with oil in 1892. Since then there has been a tremendous increase in the use of oil chiefly for adulticides, but with large amounts being spread as larvicides. Stage estimated that by 1952 some 75 million gallons of oils were being used annually for insecticides in the United States, at least 1 million gallons for mosquito control.

The first record of the use of Paris green mosquito larvicide is a note by B. W. Marston, Sr., in the *New Orleans Times Picayune* of 16 February 1916, in which he states that several years previously he had found that he could control mosquito breeding in rain-barrels by using Paris green. The first comprehensive experiments were done by Barber and Hayne as reported in 1921. These followed the demonstration by Roubaud of the practical possibilities of such stomach poisons as trioxymethylene for killing mosquito larvae. From this period until the advent of DDT vast quantities of Paris green were used as larvicide, spread by hand, by blowers, and by airplanes.

Gorgas

The most outstanding early demonstration of the usefulness of anti-larval measures, particularly of larvicides, was that of William Crawford Gorgas in Havana and Panama. It was so impressive that Sir William Osler said nothing matched it 'in the history of human achievement'. Gorgas, then a major in the Medical Department of the United States Army, became chief sanitary officer in Havana, Cuba, in 1898. Fighting was over and the Spanish army had withdrawn. But forces more powerful than bayonets and bullets remained to threaten the Americans with annihilation. [illegible]llow fever, continued their [illegible] diseases had several times driven invading armies out of the West Indies and had exacted a high annual tribute from the Spanish. Malaria and yellow fever now promised to demonstrate again their formidable power. Fully four-fifths of the American soldiers

were having fevers and their stamina and morale were exhausted

Gorgas attacked yellow fever with great enthusiasm and thoroughness, sanitating Havana in the traditional way by removing and destroying rubbish and filth of all kinds Actively supported by the Military Governor, Major-General Leonard Wood, who was a physician, Gorgas gave the city the most thorough scrubbing it had ever had, indeed he believed that he made Havana cleaner than any city had ever been in all history He became a sanitary dictator But mysteriously as the city became cleaner yellow fever increased, probably because of an influx of immigrants who were fuel for the smouldering flames of the disease Certainly, traditional sanitation failed completely Yellow fever was obviously not due to filth The Surgeon General therefore sent a Yellow Fever Commission to Cuba to investigate the cause of the disease, appointing as leader Dr Walter Reed of the Army Medical Corps His associates were James Carroll, also an army surgeon, Jesse W Lazear, a physician and bacteriologist of Johns Hopkins University, and Dr Aristides Agramonte, the son of a Cuban general and a recent recruit in the United States Army Medical Corps The Commission, profiting by the demonstrations of Manson, Theobald Smith, Bruce Ross, and the Italians, and particularly by the local observations of Dr Carlos Juan Finlay, succeeded most brilliantly and thereby added another notable chapter to the history of medicine Reed and his colleagues demonstrated conclusively in 1899–1900 that yellow fever is carried by *Aedes* (*Stegomyia*) mosquitoes

On the basis of the findings of Reed's commission, Gorgas proceeded to put all yellow fever patients into mosquito-proof screened rooms Then he began to destroy the mosquitoes responsible for spreading the disease Aedine vectors of yellow fever breed in all sorts of receptacles about houses, so Gorgas organized efficient sanitary squads, called 'stegomyia brigades', which went around regularly emptying or destroying pitchers, pans, eaves gutters, flower-pots, and similar water-holding receptacles By these methods, Gorgas in five months completely freed Havana of 'yellow

jack'! From 1761 until 1901, there had been yellow fever in Havana, with deaths ranging in number from 1,282 in 1896 to 310 in the year 1900. Gorgas began his campaign in March 1901 and the last death from yellow fever was in August of that year. Except for a short outbreak in 1905, quickly curbed by renewing the anti-mosquito measures, there has not been a case of yellow fever in Havana since Gorgas made what he called his flank attack on the disease. The mysterious and deadly Minotaur had been slain. Gorgas was Theseus; Havana the labyrinth, Reed, like Ariadne, furnished sword and guiding thread.

At the same time, as a result of measures directed by Gorgas against *Anopheles* mosquitoes, the malaria case- and death-rates fell sharply and the disease no longer was a serious menace in the city.

While Gorgas was in Havana, plans had matured for the construction of the Panama Canal by the United States Government. Naturally, medical authorities suggested that Gorgas be chosen to take charge of sanitation. The forty-mile Isthmus of Panama was 'one sweltering miasma of death and disease', chiefly malaria and yellow fever. It was said to have two seasons. There was the wet season from mid-April to mid-December when people died of yellow fever after four or five days' illness, and there was the dry season from mid-December to mid-April when people died of pernicious malaria after two or three days' illness. No wonder the French had failed in an attempt to push a canal through this 'hideous dung heap of physical and moral abomination', as a contemporary author described it.

Ferdinand de Lesseps, director of the final French effort, was a practical engineer who had dug the Suez Canal. He had technical skill and financial backing but, of course, he could know little about the facts of mosquito-borne diseases when he came to Panama in 1881. For many reasons, not least because of malaria and yellow fever, de Lesseps failed in his attempt to construct the canal. Quoting a contemporary report, there were 'hardly enough trees on the Isthmus for crosses to mark the graves of his labourers'. Yellow fever and its malefic partner malaria turned expert

engineering efforts into shambles. Mosquitoes, at that time not yet exposed by Ross and Reed, here administered to man the greatest engineering defeat ever known. The losses in eight years were £52 million and 50,000 lives!

The United States Government took over from the French in May 1904, and appointed a Panama Canal Commission headed by an Admiral who was a noted engineer and canal expert. The American Medical Association asked in vain that Gorgas be made a member of this Commission. Here was an interesting situation. On the one hand was the job of digging a canal through tropical jungles known to be deadly because of yellow fever and malaria. On the other was the man whom leading scientists the world over had acclaimed for his magnificent success in controlling yellow fever and malaria in Cuba. One might presume that the services of Gorgas were eagerly solicited and that ample facilities were accorded him. But, on the contrary, the Isthmian Canal Commission would have nothing to do with Gorgas. They were definitely suspicious of a medical officer who spent time and money destroying mosquitoes instead of devoting full attention to treating the sick. So the Surgeon General of the Army in 1904 used his authority to put Gorgas in charge of the sanitary work in the Canal Zone itself, a position not within the jurisdiction of the Canal Commission. Gorgas had to report to the Governor of the Zone who, together with the Chairman of the Isthmian Canal Commission, determined to get rid of him as soon as possible. The enthusiasm of Gorgas for controlling mosquitoes was openly ridiculed and his activities were repeatedly curtailed.

In November 1904 yellow fever in Panama began to demonstrate its power once again. Death followed death. By the early part of 1905 the entire canal force was in panic, most of the officials, including the engineers, making frenzied efforts to get back home, only restrained by lack of sufficient transport. Newspapers in the United States took up the cry and the whole project of the canal was at the brink of the same chasm into which the French had plunged. The situation was desperate, considered by many hopeless.

Gorgas had his own organization and despite serious handicaps he was in fact blunting the edge of both malaria and yellow fever. Nevertheless, in June 1905, the Governor and the Chief Engineer and members of the executive committee of the Canal Commission united in recommending to the Secretary of War that Gorgas, and those with him who believed in the mosquito transmission of malaria and yellow fever, be dismissed, and that more practical men be sent to replace them. Fortunately, President Theodore Roosevelt overruled his Secretary, who had agreed with the Commissioners, and the President further directed that full support be given to Gorgas. In July 1905 Mr. J. F. Stevens was appointed Chief Engineer and he succeeded in having the Sanitary Department made a bureau of the Commission itself, so that Gorgas reported to Stevens, who gave him excellent and intelligent support. The Chairman of the Canal Commission, when about to return to the States soon after Stevens's arrival, told the latter that he and the Governor had decided to dismiss Gorgas. Stevens replied that if so he would himself go to Washington to protest and if Gorgas were removed he would himself not return to the isthmus. Apparently, this ended the question of the removal of Gorgas. In 1908, on Stevens's recommendation, Gorgas was made a member of the Canal Commission. Some years later, in 1914, Gorgas wrote to Stevens recalling their friendship and mutual understanding and he made the significant statement that Stevens had been 'the only one of the chief officials on the isthmus who always supported the Sanitary Department, and I mean this to apply to the whole ten years, both before and after your time.'

More shocking failure to profit by the experience of others than that of the Panama Canal Commission in regard to disease prevention would be difficult to find. They continued to believe, as one of the Governors said, that 'A dollar spent on sanitation is like throwing it into the bay.' It all seems incredible, although one occasionally meets this attitude even today.

The Achievement of Gorgas

Gorgas knew what to do and having obtained some authority through Stevens's support and because of a widespread fear of yellow fever and malaria, he did a superb job of sanitation Persistently and effectively he pursued the urban 'pot breeding' yellow fever mosquito until one day in May 1906 he was able to say to some young surgeons, 'Take a good look at this cadaver for it is the last case of yellow fever you will ever see in Panama ' At the end of 1905 the general death rate in the Canal Zone had fallen to 15 3 per thousand, about the same as the rate of 14 1 per thousand, in the same year in the United States By 1928 the rate was down to the astoundingly low figure of 8 53 Here was a strip of territory which for centuries had been one of the world's most deadly places, now, thanks to Gorgas and his successors, one of the most healthful!

Gorgas also attacked malaria forcefully by many methods, aided by his exceedingly able Chief Sanitary Inspector, Captain Joseph A Le Prince, who was an engineer, and by the brilliant laboratory studies of Dr Samuel Taylor Darling, and by such outstanding assistants as Dr Henry Rose Carter, of the Public Health Service According to Gorgas, the anti-malarial work in the order of its importance consisted of drainage, brush and grass cutting, oiling, use of soluble larvicide, prophylactic quinine, screening, and the killing of adult mosquitoes in the quarters of labourers

The *Anopheles* carrier in Panama bred in ponds, marshes, swamps, and standing water, so controlling this widespread rural insect was a greater problem than that of dealing with *Aëdes* and *Anopheles* in Havana Malaria was highly endemic For example, the rate in July 1906 was equivalent to 1,263 hospital admissions per 1,000 of population! But Gorgas, with his efficient sanitary organization, reduced the numbers of canal workers admitted to hospitals for malaria from a yearly rate of 821 per 1,000 in 1906 to one of 76 per thousand in 1913 Here was a superb accomplishment by Gorgas, described by Sir Malcolm Watson as 'the greatest sanitary achievement the World has seen'

As to costs, it is approximately correct that from the beginning to the official ending of construction, all medical and health work, including buildings, required about 4 7 per cent of the total cost of the canal Approximately 1 7 per cent of the total cost of the canal was spent for the prevention of disease It has been estimated that the strictly anti-mosquito work during the busiest years, 1904-14, totalled about 14 shillings ($2) *per capita* of those protected per year

A study of the records indicates that at all times at least one-third of the French labourers and staff under de Lesseps were ill in hospital The United States force averaged 39,000 men during the ten years Had it suffered from the same rate of illness, as certainly would have been the case without the sanitary measures of Gorgas, there would have been 13,000 American employees in hospital every day during the ten years from 1904-14 Actually the rate of illness averaged only 23 per 1,000 At least 12,000 men per day for ten years were kept from the need of hospitalization by Gorgas! There was a saving of at least 39,420,000 man-days of illness Since hospital care cost 7 shillings ($1) a day, here was a probable saving of £14 million ($39,420,000)

Had the same death-rate prevailed for the Americans as for the French, there would have been 71,000 more deaths among the American employees than actually occurred from 1904-14 These estimates do not take into consideration loss of efficiency, stoppage of work, demoralization, and other characters of a disease-infested project

Gorgas himself came to the following conclusion

It will not be considered an exaggerated estimate to state that eighty million dollars (£28 5 million) was saved to the United States Government by the sanitary work done on the Isthmus during the ten years of construction That is, granting that the construction work could have been accomplished under such conditions as had existed during the construction period of the old French Company, or which existed on the Isthmus of Panama at any time prior to 1904, and granting that public sentiment in the United States would have allowed the prosecution of the work with such mortality among the labouring force as had previously occurred it would have cost the

United States eighty million dollars more than it actually did cost to accomplish the results it has attained on the Isthmus

Time fogs even the brightest records Hence it does not seem amiss to recall once more the tremendous impression that Gorgas made by his sanitary victories in Havana and Panama For instance, many of the leading malariologists and sanitarians of the world undertook pilgrimages to Panama to see the work Ross in the autumn of 1904 was one of the first Incidentally, when Ross was en route to the Canal Zone, he spent several days with Osler in Baltimore One morning

the neighbouring household was aroused by shouts of delight, and saw from their windows overlooking Osler s backyard an Englishman engaged in an investigation of the various empty but water holding window boxes, flower pots, and so on, and on being questioned as to his occupation, said with glee 'I have found more mosquito larvae in the garden of the Professor of Medicine of the Johns Hopkins (School) than I expect to find in the entire Canal Zone'

Ross became enthusiastic about what he saw in the Zone Unfortunately his money was stolen in Panama and he arrived back in New York with only one dollar and no hat The Waldorf Hotel not only gave him credit facilities but also advanced funds for a new hat!

When Gorgas visited London in 1914, he received, according to Osler, the greatest ovation ever given a medical man in England Oxford University held a special convocation to confer upon him the honorary degree of Doctor of Science At home the President made him Surgeon General of the Army and the Congress made him a Major-General, at that time an almost unprecedented rank for a medical officer He served his country with distinction in this high office during the First World War and then went to South America on a yellow-fever commission, under the auspices of the Rockefeller Foundation

In 1920 in London, en route to Lagos with another Rockefeller Foundation Yellow Fever Commission, Gorgas had a paralytic stroke and was taken to the Queen Alexandra Military Hospital There, from the hands of King George V

he received the insignia of Knight Commander of the Most Distinguished Order of St. Michael and St. George.

A few days later he died and was given in St. Paul's Cathedral an official state funeral of a British Major-General, one of the most significant honours that Britain could bestow. On the casket lay a solitary wreath sent by Sir Patrick Manson. Although these two great men had never met, they had corresponded with mutual respect and admiration. Later the body of Gorgas lay in state for four days in Washington, and at the services of the Church of the Epiphany an illustrious assembly gathered to pay tribute to this man whom *The Lancet* called 'the best known and most uniformly successful medical administrator not of his age alone but of any age'.

11

PROPHYLAXIS AGAINST ADULT MOSQUITOES

THE most effective and most popular method of controlling malaria today is the killing of adult mosquitoes of vector species inside houses, a measure that, in its simple hand-slapping form, was very likely the earliest weapon man employed against mosquitoes Quite probably the next step in

insecticidal residual spraying which is rapidly clearing malaria out of entire countries Here is a world-wide development as spectacular as any in all the history of prophylaxis against human disease

A third control method that must have come into use very early is the application of repellents to the skin Mud, pitch, ashes, bark infusions, and the leaves of certain plants were probably the first repellents—forebears of modern chemicals like dimethylphthalate, developed during the Second World War We infer this early use of repellents because primitive peoples today commonly smear their skin with substances that they hope will give some protection against insect bites Of course, such simple repellents are not very effective, nor were most of the 1,001 proprietary preparations submitted for testing in recent years Mosquitoes are pertinacious and not easily discouraged Prior to 1940, the most widely used culicifuge was probably oil of citronella, one application of which was effective for about fifteen minutes There are now several that will give protection against anophelines for as long as four hours, for example, a mixture called 6-2-2 and consisting of sixty parts of dimethylphthalate and twenty each of indalone and

Rutgers-612 (2-ethyl-1, 3-hexanediol) But here is rather a small gain to show for centuries of effort

Other early practices to outwit mosquitoes were sleeping in elevated places and using protective nets One witness was Herodotus of Halicarnassus (*c* 484–425 B C), who, in describing Egyptian customs, wrote (Book II, Chap 95)

> The contrivances which they use against gnats, wherewith the country swarms, are the following In the parts of Egypt above the marshes the inhabitants pass the night upon lofty towers, which are of great service, as the gnats are unable to fly to any height on account of the winds In the marsh-country, where there are no towers each man possesses a net instead By day it serves him to catch fish, while at night he spreads it over the bed in which he is to rest, and creeping in, goes to sleep underneath The gnats, which, if he rolls himself up *in his dress or in a piece of muslin, are sure to bite through the* covering, do not so much as attempt to pass the net (Rawlinson's translation)

A still earlier report is in the perhaps fictitious Apocrypha It tells us that when Judith was introduced to one of Nebuchadrezzar's generals, Holofernes (6th century B C) whom she killed, the warrior was 'lying on his bed inside the mosquito curtain which was of purple and gold, with emeralds and other precious stones interwoven' (Judith x 21)

The *rete* or nets that the ancients used for hunting and fishing were often made of flax, occasionally of hemp or even of palm fibres The meshes or *maculae* were great or small, depending on the needs A drag-net, or *sean*, our seine, might have, for example, very small apertures Such netting, hung over beds and couches to keep away flying insects, constituted a gnat-curtain or *conopeum* (from the Greek word meaning gnat) These bed-nets were noted by several early writers, as for instance by Varro in *Rerum rusticarum* (II 10 VIII) This author was discussing the advisability of selecting able-bodied women as companions for shepherds He quoted his friend Atticus as having remarked to him 'I have heard you say that when you went to Liburnia (Croatia) you saw there Liburnian housewives carrying logs, and at the same time children, whom they

were suckling, thus proving how feeble and contemptible are our modern newly delivered mothers, who lie for days inside mosquito nets' 'True it is,' replied Varro

The fact that *conopea* stemmed from Egypt, and that they were used in Rome to protect women and children, probably explains why Propertius (*c* 50–15 B C) called them *foeda*, i e foul or disgraceful (III 11 45), and Horace (65–8 B C) wrote (Epod ix 16) 'And among the military standards, oh, shame! the sun sees a mosquito curtain' Obviously, here was 'Oriental effeminacy' at its worst! Even today, in and out of the Armed Forces, one occasionally meets strong men suffering from this proud but treacherous *conopea-phobia* of Horace and Propertius

Later, Juvenal (*c* 60–120) wrote (iv 80) that nets gave protection over the cradles of rich and noble babies Thereafter, mosquito curtains seemed to acquire a measure of respectability, for we find Paulus Silentiarius (*fl* 562) commenting that they were useful during a post-prandial siesta because they obviated the need to keep slaves busy with fly-swatters

Marco Polo in the thirteenth century described nets he had seen in south India He wrote (as edited by Kromroff, p 289)

> The natives make use of a kind of bedstead or cot, of very light cane work so ingeniously contrived that when they repose on them, and are inclined to sleep, they can draw close the curtains about them by pulling a string This they do in order to exclude the tarantulas, which bite grievously, as well as to prevent their being annoyed by fleas and other vermin, whilst at the same time the air, so necessary for mitigating the excessive heat, is not excluded Indulgences of this nature, however, are organized only by persons of rank and position, others of inferior class lie in the open streets

Nets were used in Virginia in the seventeenth century, to judge from Blanton's discovery of an inventory of 1684 in Henrico County, that included 'two pieces of Mosquito Cloath'

James Johnson in 1827 quotes the following anecdote from Regaud de l'Isle, probably referring to the early part of the nineteenth century

During my residence near the marshes of Languedoc, I lived near a very fine building, formerly the convent of Franquevaux, erected on the very border of the marshes The monks in this house were perfectly healthy the year round, though few of the inhabitants of the environs escaped disease in summer and autumn Tradition never theless relates that they were accustomed, in hot weather, to sup on a terrace contiguous to the convent—a sure method of exposing themselves to disorders, but they were sheltered by a tent of double or triple canvas, and this simple precaution, requisite against the mosquitoes proved, unknown to them, a still more certain protection against the miasmata

Gordon Pasha and Emin Pasha, according to Felkin, always used mosquito nets The first-named said that nets acted as filters against the malarial poison as well as against mosquitoes and other insects which he thought might cause fever

Sykes in a letter to the *British Medical Journal* in 1898 quotes from an 1834 medical textbook a recommendation that one should sleep under a fine mosquito net wherever intermittent fevers are common

In the mid-nineteenth century the wife of the first Bishop of Capetown made a mosquito net which she gave to David Livingstone for use in Central Africa He sent back a letter that began as follows

14 July 1863

My dear Lady,

I feel exceedingly obliged by your kindness in making such a beautiful mosquito curtain for me Beyond a doubt it is the hand somest that ever appeared in this country, and I am a great admirer of the invention

In his last journals, published in 1874, Livingstone wrote

Camp sweet and clean, but it, too has mosquitoes from which a curtain protects me completely in a great luxury, but unknown to the Arabs to whom I have spoken about it Abed was overjoyed by one I made for him others are used to their bites as was the man who said that he would get used to a nail through the heel of his shoe

The use of mosquito bars for malaria prevention was first recommended in the U S Army in 1898 by Major J R

Kean, in Havana General orders to this effect were issued in the Department of West Cuba in 1900.

Protecting skin from night biting anopheline vectors of malaria was a method of preventing agues, sometimes advised even before the insect was visualized as the infecting agent Several observers so intelligently described this and other precautions against ague that in their comments we could substitute 'malaria carrying mosquitoes' wherever they use the words 'miasmata', 'marsh vapours', 'night airs', 'fogs', or 'dews', and the passages they wrote would make good sense today Such a writer was Thomas Winterbottom, Physician to the Colony of Sierra Leone, who wrote in 1803 in reference to preventing fevers that 'Those who are exposed to the night air should put on additional clothing ' He recommended 'trowsers reaching to the ancles and fastened by strings or buttons' It is interesting to read further in his *Medical Directions for Use of Navigators and Settlers in Hot Climates*, as quoted by Elliott For example,

One of the most important means of preserving health in a hot climate is by going early to rest Early rising so much recommended in colder countries does not seem to be attended with the same advantages between the tropics the coolness of the morning is grateful, but the heavy dews which fall before sunrise and the thick fog which frequently lies upon the ground till the sun is risen render the beginning of the day unwholesome more especially in uncultivated or marshy places

We now know that many vectors of malaria feed during the morning as well as the evening twilight

Winterbottom continued,

It has also been sufficiently proved that there are certain causes which in every country, especially in warm climates will produce fever The most common and also the most fatal of these causes is the vapour arising from swamps and marshes or spots of ground, partly covered with mud and partly with water (Though the most common cause of fever in hot climates be the air which blows over marshes yet when the fever is once introduced among a number of people it is very apt to become infectious and spread where the original cause does not reach) Persons living to windward of a

marsh or swamp, though at no great distance from it, may enjoy a good state of health, but if they are to leeward of it even at a considerable distance, their situation will certainly prove unhealthy It is not easy to say at what distance from a swamp the wind which blows over it loses its harmful qualities, we have however reason to suppose the distance is at least a mile Persons living to leeward of a marsh, and at no great distance have often had their health preserved by trees growing between them and the marsh

Winterbottom tells navigators that

> It has often happened in fleets lying at anchor off a swampy shore that ships nearest to it have proved very unhealthy, while the *crews of vessels distant from it a mile or more remained in perfect* health When the side of the ship is exposed to the wind from the shore, the ports on that side should be kept constantly closed In such situations also it will be found of much use to smoke the ship frequently between decks this may be done by burning tobacco, junk gunpowder, etc in a common iron pot, or by carrying a fire into different parts of the ship. the dampness of the air is thus most effectually destroyed and to the moisture of the air, we must refer a great part of its harmful effects The crews of boats employed in wooding or watering who stay all night on shore or remain there some time after sunset, are very frequently cut off by fevers The bad effects of their exposure in an unhealthy country do not always immediately appear, they are sometimes not felt in less than a week or ten days after leaving the place and getting out to sea

Finally, the observation was made that

> The signs of an unhealthy country are great swarms of flies mosquitoes &c, thick fogs lying on the ground for sometime after sunrise, heavy dews cold nights succeeding very hot days Healthy situations are those where the soil is dry and elevated as upon the sides or summit of a hill at a distance from marshes or stagnating waters In general places open to the sea, bordered by a sandy or gravelly beach free from slime and ooze, are preferable to all others

Adulticides

As already stated, the most useful malaria prophylactic measure today is the killing of adults of the vector species of *Anopheles* within houses by residual spraying with DDT or similar organic toxicants This method has evolved from

primitive mosquito destruction by hand and by fumigation, traps, and by space-spraying with pyrethrum

At first, of course, the motive for killing mosquitoes was simply to obtain protection from mosquito bites After the discoveries of Ross and the Italians and the observation that many species of malaria-carrying *Anopheles* prefer to roost by day inside habitations in places accessible to man, it became obvious that some malaria control benefit might derive from the destruction of infected mosquitoes in their resting places Ross, for example, recommended the use of small hand-nets to destroy mosquitoes in houses He suggested that boys might be employed at a wage of 'a penny for fifty Anophelines' He said that Sir William MacGregor employed a boy to kill mosquitoes in this way in Lagos in 1901 Nuttall and Shipley in 1902 wrote 'We are moreover inclined to believe that suitably coloured boxes, or colour traps, might be of practical utility in and about houses infested with mosquitoes'

Gorgas and Le Prince in Panama regularly employed men to catch and destroy adult mosquitoes 'Killing mosquitoes in quarters' was listed as one of the control measures in the anti-malarial work during the construction of the canal Gorgas said that by using this method 'most of the infected mosquitoes are killed before they become infectious' He added that, 'It is surprising what results can be obtained by this method in properly selected cases' Le Prince also spoke highly of the measure He devised the use of test-tubes containing cotton wool soaked with chloroform, a procedure 'quieter than the slapping method' and more effective

In 1927 the Malaria Commission of the League of Nations recommended that an active endeavour should be made wherever possible to *induce householders, especially housewives*, as part of their daily cleaning tasks, to kill adult mosquitoes found within houses

Fumigation was an early extension of the primitive smoke smudges In Homer's Odyssey (1000 B C) it is written 'But to his dear nurse Eurycleia said Odysseus "Woman, bring sulphur, a protection against harm, and bring me fire to fumigate the hall " At these his words, his dear nurse

Eurycleia did not disobey, but brought the fire and sulphur. Odysseus fumigated all the hall, the buildings and the court' (xxii. 470–501. Palmer's translation, p. 357).

In 1865 E. H. Parkes, first Professor of Military Hygiene in the Royal Army Medical School, stated that carbolic acid vapour killed fleas, moths, and gnats. He suggested that it would also prevent the development of malaria—meaning the miasma not the disease, but he said that it would not be possible to use it on the necessary scale. Parkes, in 1871, quoted Dr. S. Meredith as having noted that 'the charcoal burners of different tea-gardens in Assam, who live near the pits and the charcoal and who breathe an air strongly impregnated with the smoke and other products from the burning, rarely suffered from malarious complaints'.

Other fumigants used against mosquitoes have been formaldehyde, tobacco, cresol, chlorine, and pyrethrum.

Traps have occasionally been tried in efforts to reduce malaria vector incidence since they were first suggested by Nuttall and Shipley in 1902. They are now chiefly employed to sample mosquito populations in order to survey density or species distribution.

Pyrethrum

There is a chrysanthemum in Dalmatia, growing in the fields like a small daisy. The flower of this indigenous plant, *Pyrethrum cinerariaefolium*, contains active principles, called *pyrethrins* and *cinerins* that are deadly to many insects, including mosquitoes. The use of pyrethrum flowers for insecticidal purposes, probably at first against lice and fleas, seems to have originated in Persia some centuries ago. In the *Arabian Nights* there is a reference to it. The powder was first manufactured in Europe in 1828 and introduced in the United States in 1860. Consumption of pyrethrum in the States increased from 600,000 pounds in 1885 to 3 million pounds in 1919. In 1949 F. B. La Forge and associates, of the Department of Agriculture, synthesized the allyl homologue of cinerin. This product, called *allethrin*, vindicates the thesis that synthetic insecticides can be made that rival natural insecticidal products of certain plants.

At first the chief use of pyrethrum was as a powder, sometimes burned slowly as a fumigant but usually dusted Kerosene extracts of pyrethrum were first used for controlling [illegible] on pyrethrum-kerosene sprays in 1923 but it was held invalid in 1930, as it was said that the U S Navy had used such sprays (e g Flyosan) against insects in the First World War Greatly increased use of the sprays followed this ruling and they soon came to be considered as household necessities in many areas, as in the south-eastern States By 1935 over 16 million pounds of pyrethrum flowers were being imported yearly into the United States, almost entirely for the manufacture of kerosene extracts for private household spraying against mosquitoes and other insects The plant was being grown commercially in Japan, British East Africa, and the Belgian Congo

Apparently, G Giemsa and P Muhlens in 1911–12, using solvents such as alcohol but not petroleum oils, were the first to publish the result of experiments in the use of pyrethrum sprays for mosquito control Andrew Balfour in 1913 reported the use at Khartoum of Giemsa's 'Mucken' fluid, consisting of a tincture of pyrethrum, soft soap, and glycerine, diluted 20 to 1 with water Lefroy's fluid was used by the British Army to some extent in the First World War It consisted of pyrethrum, methyl alcohol, and other ingredients, diluted with water or soap solution

S L Brug and J van Slooten in 1927 published a report of some experiments on the efficiency as insecticides of such commercial preparations as 'Flit', 'Rids', and others Holt and Kintner made favourable reports in Manila in 1932

At the Pan-African Health Conference of the Health Organization of the League of Nations, in November 1935, Dr G A Park Ross, Senior Assistant Health Officer, Union of South Africa, and Dr [redacted] De Meillon of the Department of Entomology, South African Institute for Medical Research, presented reports on their experiences with pyrethrum-paraffin spraying of adult mosquitoes in habitations,

the first systematic killing of vector anophelines in houses with pyrethrum-petroleum oil sprays. This work inaugurated the modern era of nation-wide malaria control.

Park Ross was faced with a series of severe summer epidemics of malaria transmitted by *A. funestus* and *gambiae* in Natal and Zululand, beginning in 1929. He was unable to control these outbreaks with larvicides plus quinine. In 1930–1 pyrethrum insecticide was used in a few isolated instances by certain employers. Then, during the 1931–2 season, *systematic house-to-house spraying with pyrethrum* insecticide was organized in one village, and incidental use was made of the same preparation in other places. It became evident that not only was the method effective, it was also welcomed by the local people, and was cheap and easy to apply. So, in the 1932–3 season, a weekly spraying of all dwellings with pyrethrum insecticide was the preferred *method of attack in many parts of the affected area.* Some larviciding and the use of quinine continued. The results were so good that in the 1933–4 season, the spraying measure became standard for the entire area.

Park Ross concluded that, 'When spraying is started as soon as anopheles begin entering huts, and kept up through a season, no epidemics have occurred, in spite of the continuance of anopheles-breeding.' He had no hesitation in warmly recommending the method and was supported by De Meillon. The latter noted the most important point, still sometimes overlooked, that, 'the whole idea underlying malaria control by anti-adult measures' is that 'it is not intended to destroy all *A. gambiae*, but only those which are infected, which past experience has shown are largely to be found indoors'. De Meillon also noted that the anti-adult spraying cost only about a third as much as the anti-larval work and was more effective.

In 1934 a note by Swellengrebel on pyrethrum spraying of adult mosquitoes in the Netherlands was circulated by the Malaria Commission of the League of Nations. Swellengrebel also published a paper on the subject in the same year. In India, Covell, Mulligan, and Afridi of the Malaria Survey (now Institute), carried out experiments with the

same method in Delhi in 1936 and 1937, with highly satisfactory results in four selected communities in the urban area and two villages on the periphery They concluded that 'the results suggest that this method is likely to prove of great value in India, especially in the case of isolated communities where anti-larval measures are impractical, and where the vector species of anopheline rests in dwelling places in the daytime' Costs were low, much lower than corresponding costs for control by larviciding

Then came further tests with pyrethrum spray-killing of adult malaria vectors in South India where the author with F W Knipe and T R Rao, found the method highly satisfactory against *A culicifacies* So, at last, here was a method of malaria control that not only was welcomed by the people but was cheap enough to be practical even in rural India In 1936 I had been forced to conclude that no measure of malaria control had been demonstrated that was economically feasible for rural India or much of the rural tropics, generally Now we had a method that would completely stop the transmission of malaria in certain rural tropical areas, at a cost of less than 10 cents *per capita* per year During the Second World War considerable use was made of pyrethrum spraying against adult mosquitoes For example, no fewer than 40 million 1-lb aerosol pyrethrum 'bombs' were purchased by the Armed Forces These containers employed a liquefied gas—dichloro-difluoro-methane —which on release instantly vaporized and carried pyrethrum insecticide into the air as a space spray against mosquitoes

DDT

Dichloro-diphenyl-trichloroethane was first synthesized by a Viennese pharmacist, Othmar Zeidler, while studying chemistry in Strasbourg in 1874 But its insecticidal properties were not discovered until 1939 when the dye-manufacturers, J R Geigy Co in Switzerland, were searching for a chemical to kill clothes moths One of their research workers, Paul Muller, resynthesized Zeidler's compound and discovered that it had amazing power to kill certain

insects, an observation for which in 1948 he received a Nobel Prize During 1942 some 150 tons of the compound were used in Switzerland in the form of 'Gesarol' against agricultural pests, particularly the potato beetle Another formulation of the same insecticide was called 'Neocid' and had special value as a lousicide This fact was noted by Major A R W de Jonge, United States Military Attaché in Berne Largely through his interest samples were sent to the United States and to the United Kingdom in 1942 Tests fully confirmed Muller's claims of insecticidal usefulness Dr H L Haller in the Beltsville, Maryland, laboratories of the Department of Agriculture analysed the samples and synthesized the active ingredients Large-scale manufacture was developed with considerable speed in both the United Kingdom and the United States Nine and a half million pounds of DDT were produced in the United States in 1944 and over 47 million pounds in 1947 The now universally accepted name, DDT, was first applied by the British Ministry of Supply in 1943

DDT kills some insects on contact, others as a stomach poison when they swallow it Special importance stems from its prolonged *residual* killing effect when sprayed on surfaces upon which insects later walk or rest, as first noted in 1942 for house-flies by Wiesmann, one of Muller's colleagues, and as first suggested for mosquitoes by A W Lindquist in late 1942 and tested by himself, Gahan, and colleagues at the Orlando Laboratory of the United States Bureau of Entomology in 1943 In Orlando, the larvicidal value of DDT against anophelines was also demonstrated This laboratory, under the direction of F C Bishopp, W E Dove, and E F Knipling, studied DDT intensively With a staff of over thirty scientists, it contributed greatly to our knowledge of the insecticide

DDT does not kill mosquitoes more quickly than does pyrethrum but, unlike pyrethrum, it continues to kill for months after it has been applied to a surface where mosquitoes come into contact with it Pyrethrum is a space-spray and in practice only those insects touched by the insecticide at the time of spraying are destroyed Hence, to

kill malaria infected anophelines before they become infectious, pyrethrum is used once a week because it takes only a little longer than that time for sporozoites to develop in a mosquito Moreover, unless the insects are exposed at the time and in the place of pyrethrum spraying they are not killed Some vector anophelines enter houses at night for meals of human blood and then leave at daybreak, or earlier, for daylight resting places not accessible to spraying But DDT need not score a direct hit on the insect It can be sprayed on surfaces in anticipation that vector mosquitoes will rest there at some time during the period of ten days or so when they are incubating sporozoites Moreover, one spraying may be sufficient for an entire season Both DDT and pyrethrum spraying are relatively inexpensive and have been popular with householders

Another residual insecticide is *benzene hexachloride* (BHC), said to have been prepared by Michael Faraday in 1825 But its insecticidal properties were discovered in the United States in 1933, and independently in France in 1941 and in England in 1942

Somewhat similar is *chlordane* (sometimes spelt chlordan), developed by a different method devised by Otto Diels and Kurt Alder, Germans who received the Nobel Prize in chemistry in 1950 for their achievements in this general field Their new synthesis had wide significance Two more recent, related insecticides have been named *dieldrin* and *aldrin*, in honour of these chemists Chlordane and dieldrin are proving useful in malaria control, so that with DDT and BHC we now have four good residual toxicants for use against *Anopheles* adults

12

THE DDT ERA

THIS is the DDT era of malariology. For the first time it is economically feasible for nations, however underdeveloped and whatever the climate, to banish malaria completely from their borders. The special influence of DDT and similar toxicants, such as BHC (benzene hexachloride, gammexane) chlordane, and dieldrin, on the epidemiology of malaria is derived from the fact that, as previously suggested, once applied in a suitable formulation, they will for many months remain effective destroyers of the anopheline malaria vectors. Obviously, if a sufficient number of the adults of a vector species acquire lethal doses of insecticides before the period of sporozoite development ends, then the transmission of malaria in a community will be interrupted. Until the sporozoites are ripe the mosquito is not infective. Any measure that destroys infected vectors before they become *infective* will cut off transmission whether or not it reduces measurably the total density of vector adults or larvae. Residual spraying in most cases effectively prevents day or night house-haunting *Anopheles* from living long enough to become dangerous.

Today, probably no malarious country is without at least some help from residual spraying and in a number of instances the results have been amazingly successful.

Central America

Malaria has been a prime source of illness and death in Central America for many years. In some areas the disease affected 75 per cent. of the population and might result in mortality rates as high as 432 per 100,000 persons. Now the governments of the six republics, and of the territory of British Honduras, embracing a population of some 9 millions, have united in co-operation with the World Health

TINCTURA CINNAMOMI.

℞ Cinnamomi P. sescunciam,
Spiritûs vinosi tenuioris M. libram unam.

DIGERE sine calore, et cola.

TINCTURA CORTICIS PERUVIANI simplex.

℞ Corticis Peruviani P. uncias quatuor,
Spiritûs vinosi tenuioris M. libras duas.

DIGERE, et cola.

TINCTURA CORTICIS PERUVIANI volatilis.

℞ Corticis Peruviani P. uncias quatuor,
Spiritûs salis ammoniaci M. libras duas.

DIGERE sine calore in vase bene clauso, et cola.

TINCTURA FOETIDA.

℞ Asæ fœtidæ P. uncias quatuor,
Spiritûs vinosi rectificati M. libras duas.

DIGERE, et cola.

TINCTURA

FIG 14 The first reference in the London Pharmacopoeia to the use of Peruvian bark

Courtesy of the Wellcome Historical Medical Museum

FIG 15 Ancient Sicilian coin commemorating Empedocles

Courtesy of the British Museum

Three coins were issued by the Selinuntines to honour Empedocles The one above depicts Apollo and Artemis side by side The former is discharging arrows from his bow to slay the pestilence Artemis represents the women of Selinus who suffered so severely from the disease that Empedocles controlled On the other side of the coin the River god Selinus with short horns holding a phiale and lustral branch is sacrif c ng at an altar in front of which is a cock Behind him on a pedestal is the figure of a bull possibly representing the previously untamed river Above the bull is a selinous leaf

Organization, the Pan-American Sanitary Bureau, and the United Nations Children's Fund in a project designed to stamp out this and other insect-borne diseases by the application of modern insecticides The programme was inaugurated in 1950 and has already had striking success in reducing the incidence of malaria

Venezuela

Doctor Arnoldo Gabaldon in Venezuela appears to have been first in the world to capitalize on the combination of a sound epidemiological understanding of malaria in a country and a full appreciation of the possibilities inherent in DDT *Under his guidance in 1945 there was formulated the first* national project that from its inception was designed to eradicate malaria from an entire country by DDT residual spraying DDT was in use by civilian authorities in 1945 in several parts of the world, but no other scheme up to that time had announced as its goal 'total malaria elimination' by the new method

Venezuela is a tropical country in which malaria used to be the most important public health problem Now, thanks to eight consecutive years of DDT residual spraying, malaria is becoming an infrequent disease In most cases, two sprayings a year have been sufficient, but in a few areas one more has seemed necessary The cost has averaged from 51 to 65 (U S) cents *per capita* per year The principal vector, *A darlingi*, has disappeared from most of the sprayed areas While the density of *albimanus*, another vector, has not been much changed, the insect has been prevented from transmitting malaria

Only in two places has malaria seemed to resist DDT In one case, *Anopheles nũnez-tovari* and in the other case *A albitarsis*, both as secondary vectors, appear to have continued to transmit vivax malaria by outdoor biting, sheltering in outdoor resting places, and being thus inaccessible to DDT These areas are being dealt with by other measures, such as the use of larvicides and of carefully focused chloroquine mass treatment

British Guiana

British Guiana is a tropical country of about 83 000 square miles and 425,000 population, nearly nine tenths living in a coastal plantation fringe 5 to 10 miles wide and about 200 miles long Until recently, malaria has been the chief public health problem, even in the capital city of 93,000 people DDT was first used experimentally in 1945 with results so good that in 1947 a colony-wide systematic DDT residual spraying programme was begun under the direction of Dr G Giglioli and the joint auspices of the Medical Department and a well-organized sugar-cane industry By the end of 1950 some 98 per cent of the entire population of British Guiana was being protected from malaria by DDT As a direct consequence malaria is now uncommon The general death-rate had fallen from 25 8 in 1938 to 13 3 in 1949 In one area the spleen index in a community of 85,000 dropped from 42 5 in 1943–5 to 3 3 in 1949–50, while the parasite rate fell from 51 0 per cent to zero Costs have varied from 35 to 45 (U S) cents *per capita* per year No anti-larval measures have been carried out since 1945

Brazil

Brazil has long had serious malaria problems, with five species of vector anophelines and varied epidemiological and climatological conditions A National Malaria Service was created in 1941 and has been carrying out, under Dr Mario Pinotti, one of the greatest DDT residual spraying projects in the world Some 3 million houses have been sprayed annually and some 20 million people thus protected from malaria In most areas only one spraying a year is required The cost is averaging about 50 (U S) cents per year *per capita* of population protected or about 21 cents per year *per capita* of Brazil's total population

The results have been excellent, regardless of vector species involved For example, in eleven typical localities the total malaria morbidity in 1945 was 14,782, but this had fallen to only 1,192 in 1949 Malaria has almost been

eliminated from certain areas and beyond doubt DDT residual spraying has been a most useful measure

Elsewhere in South America

Between
malaria by
of Malaria
for Northern Argentina

DDT spraying projects are also in progress in Bolivia, Peru, Ecuador, Colombia, French and Dutch Guiana Probably some 75 per cent of all houses in malarious areas of South America are being treated For the first time there now exists for malaria control a single efficient and economical method of attack which can be standardized and applied with confidence to malarious areas throughout the Americas

Italy

Malaria eradication in Italy, including not only the mainland but also Sicily and Sardinia, is almost complete No malaria deaths have been recorded since 1948 when there were only four Among 42 5 million people, some 550 cases of malaria, mostly relapsing, were reported in 1951, and only one case in 1953 This is in contrast to 303,057 cases with 8,407 deaths in 1919 and 411,602 cases and 386 deaths in 1945

This notable achievement in Italy is the result of (1) sixty years of basic malaria research, (2) comprehensive understanding of local malaria epidemiology, (3) extensive teaching of malariology and training of specialized personnel, (4) major drainage projects and many anti-malaria activities prior to the Second World War, (5) a nation-wide malaria eradication project with residual DDT

No anti-larval measures have been carried out in Italy, except in Sardinia, since 1946

When the late Professor Alberto Missiroli, in 1946, announced his five-year plan for the eradication of malaria from all Italy there were many sceptics, but today the goal seems near at hand At yearly costs of about 50 (U.S) cents

per capita, for one residual spraying just prior to each season, a highly malarious country has been almost freed of the disease

In Sardinia, a special experiment was attempted to find out if it would be economically feasible to eliminate malaria by eradicating the vector Malaria was certainly eliminated, as described in a later section, with great benefit to the people, but a few foci of the vector, *A labranchiae*, remained at the end of the experiment and these have persisted The costs of malaria control by this method of attempted vector eradication were four times greater *per capita* than those on the mainland where equally successful malaria elimination was achieved

Cyprus

In 1913, at the time of Ross's visit, Cyprus had an overall spleen index greater than 25 per cent Highly endemic con ditions prevailed up to and through the Second World War But in 1946 there was set up an *Anopheles Eradication Campaign* based not on DDT residual spraying but chiefly on a very thorough DDT larviciding programme This project ended 10 January 1950 The cost of the four years' attempt to eradicate all anophelines from Cyprus came to about 50 (U S) cents *per capita* per year The campaign did not suc ceed in totally eradicating *Anopheles* mosquitoes, for *superpictus* and *multicolour* have persisted Nevertheless, as in Sardinia, so in Cyprus, the result was the elimination of malaria as a public health problem—a remarkable achievement, under the guidance of Dr H Shelley and Mehmed Aziz Bey

Greece

In 1910 it was estimated that a third of the people of Greece suffered each year from malaria In epidemic times, as in 1905 and again in 1942, more than half the population might be affected When the Allies went back into Greece in 1945 an experimental DDT spraying project was set up by United Nations Rehabilitation and Relief Administration (U N R R A) under Colonel D R Wright, with the notable assistance of such well qualified Greek malariologists as

Professor G A Livadas To the residual spraying was added DDT airplane larviciding of some 90,000 acres The project continued to have aid from foreign missions including World Health Organization (W H O), American Mission of Assistance to Greece (A M A G), Economic Co-operation Administration (E C A), and Mutual Security Agency (M S A)

The results of the spraying were so good that the programme was steadily expanded until, in 1947, every town, village, and hamlet in every malarious area of Greece was given residual DDT spraying, a total of some 5,821 communities, having a population of 3,514,333 In the larger towns, houses in the central portions were not sprayed if circumstances made this saving logical Excluding some of the cost of the expensive airplane larviciding, the yearly *per capita* costs of DDT residual spraying averaged less than 30 (U S) cents for the years 1946–50

Malaria deaths in Greece are estimated to have fallen from 8,000 in 1905, 1,856 in 1942, to 36 in 1949, and only 14 in 1950 Infant parasite indexes have been almost zero since 1947 Results, in fact, have been so good that in 1951 and 1952 routine spraying was discontinued in the Peloponnese and Crete and, in 1953, also in other areas Careful observations were made to determine whether or not this saving would result in any increase in malaria or malaria vectors It did not, and the experiment has indicated that once a country has reduced malaria to a low point it may be possible to curtail the use of residual sprays, applying them only in alternate years or perhaps every third or fourth season Of course, a careful watch must be maintained for dangerous foci of vectors or of gametocytes, and these must be controlled

Mauritius

Prior to 1850 there was apparently no malaria in Mauritius But soon thereafter both *Anopheles funestus* and *gambiae* appear to have been introduced from Africa and in 1867 there was a severe epidemic The capital city of Port Louis suffered so intensely that there were some 6,000 malaria

deaths in a single month among a total population of only 47,000 The disease became endemic throughout the 720 square miles of the island, and there were areas of high infection, with yearly seasonal epidemics Vector density was unusually heavy, as many as 1,500 adult *funestus* sometimes being captured in a single room in houses along the coast

In 1948 the Government of Mauritius, in co-operation with the Colonial Insecticides Committee, decided to attempt the total elimination of malaria from the island The first objective of the scheme was the eradication of the two vectors by residual spraying, which was begun in January 1949 Various formulations of DDT and of gammexane were used in order to find out which would be most effective The latter was given up for economic reasons as its brief residual effect necessitated several sprayings a year All domestic resting places of *funestus* and *gambiae* were treated Complete sprayings were done in 1949, 1950, and 1951 Spleen rates have fallen from 34 8 per cent in 1948 to 2 5 per cent after the third spraying in 1951 and now to practically *nil* Parasite rates have gone from 9 5 to 0 05 in 1952 Malaria notifications dropped from 46,395 during 1948 to 1,225 in 1951, and only 23 in 1952 General death rates (all causes) for the island declined from a mean of 27 2 per 1,000 of population in the period 1934–48 to 14 8 in 1952, and the infant mortality fell from 150 0 in 1934–48 to 80 8 in 1952, a result certainly due in large measure to a sharp decline in malaria incidence

By the end of the summer in 1950, under the direction of Dr M A C Dowling, spraying, chiefly with DDT, had obviously reduced malaria to a low level, and by 1953 chills and fever in Mauritius had become uncommon DDT greatly affected *A funestus* which became difficult to find in either larva or adult stage after two years of spraying But the other vector, *A gambiae*, although no longer taken in sprayed houses, could be found in large numbers as larvae in the breeding places or as adults in cowsheds and in new, unsprayed houses So a programme of larviciding by oiling was added to the scheme in October 1950 This reduced

temporarily the incidence of *gambiae* larvae, but the combined project has certainly not eliminated the species, which persists in fairly large numbers, so that attempts to eradicate it have been abandoned. But *funestus* has disappeared; in fact, no specimen, adult or larva, of the latter species was found between December 1950 and January 1953. The present plan is to continue a modest and economic selective programme of house-spraying and larviciding in order to conserve the absence of malaria transmission.

The Mauritius scheme has averaged in cost about 3 shillings (42 (U.S.) cents) *per capita* per year, which is not a high price to pay for the extirpation of malaria as a public health problem.

Ceylon

Malaria has been a serious public health problem in Ceylon for centuries and it is believed responsible for the depopulation of some areas in times past. DDT residual spraying was first used experimentally in 1945–6. A nation-wide scheme was set up in 1946–7 under the direction of Dr. S. Rajendram, and the results have been astonishingly good. More than half a million houses are being sprayed each year, protecting directly and indirectly some 4·8 million people, practically all of those who live in areas of endemic malaria. Costs in 1952 were only 9 (U.S.) cents *per capita* of those protected directly and indirectly. Malaria morbidity rates have fallen from 574 per 1,000 in 1940 and 413 in 1946, to 58 in 1951, 34 in 1952, and 11 in 1953. The island-wide spleen rate in 1936 was 30·6, but it was 10·3 in 1947 and had fallen to 0·8 in 1951, 0·6 in 1952 and 0·3 in 1953. In July of 1951 some 3,955 infants were examined, well distributed throughout previously malarious areas. Not a single positive smear was found. In September 1953 the infant parasite rate, 5,718 examined, was 0·1 per cent. The island-wide parasite index in 1953 was only 0·09 per cent., in contrast to 5·1 in 1939. Infant mortality rates in 1951 had fallen to about half what they were in 1938, i.e. from 161 to 82.

In 1952, rainfall in general was below normal. Thus

conditions were favourable for the river pool-breeding vector, *A. culicifacies*, and were such that an epidemic of malaria could have been predicted on the basis of previous history, as in the devastating experience of 1934. But, under the influence of DDT, malaria incidence continued to decline.

India

Malaria has long been the most serious public health problem in India. Sinton in 1935–6 estimated the malaria morbidity at 100 million cases annually, with 1 million deaths. As recently as 1952, some 80 million cases are believed to have occurred in India, with 800,000 deaths directly due to malaria and an equal number indirectly. The Malaria Institute recently estimated a loss of 171 million work-days directly due to malaria among the agricultural population of India every year! This enormous loss was conservatively calculated on the basis of a single attack per malaria case and a loss of only three days per attack.

Thanks to the Malaria Institute, under the successive direction of Sir Rickard Christophers, of Brigadier J. A. Sinton, of Sir Gordon Covell, and of Colonel Jaswant Singh, the epidemiology of malaria has been well studied and much training of personnel accomplished. Some outstanding malaria-control projects were carried out in Delhi and Bombay cities and on certain tea gardens, and there were areas under prophylaxis in Mysore and elsewhere. But relative to the total problem, little progress in malaria control had been made in India prior to 1930. The chief handicap was the relatively high cost of larviciding the malaria vectors in rural areas. Then came pyrethrum spray-killing, in Delhi and south India. This economical method was very successful when applied against a determined house-haunting species like *A. culicifacies*, but was not so useful against *A. fluviatilis* because many individuals of the latter species leave habitations after their nocturnal meals and thus are not affected by day-time indoor space sprays.

DDT was used experimentally in India by the Allied Forces in 1944 and by civilian workers in 1945. The first

major routine civilian residual spraying project was initiated in Bombay State in July 1946 and was carried forward most successfully by Drs D K Viswanathan and T Ramachandra Rao, under the State Health Department The project has been expanded each year and now includes an area of nearly ■ million habitations The annual cost is at the remarkably low level of less than 10 (U S) cents per person protected directly or indirectly Spleen rates have fallen from levels as high as 70 to percentages of 7 or below Infant parasite rates have been reduced from 15 to less than 1 per cent Viswanathan estimated that during 1952 over 1 million cases of malaria were prevented by DDT spraying which was protecting nearly 7 million persons

A collateral benefit has been the elimination of plague from Bombay State not a single case since 1948 Viswanathan also states that 15 per cent more land is now under cultivation as a direct result of malaria control

Elsewhere other projects are in progress or planned For instance, Mysore, under Dr B A Rao, has had an effective programme that is eliminating not only malaria as a problem but also plague There has been a great improvement in milk production Bhombore estimates that, all in all, for every rupee spent on DDT spraying in Mysore, there has been a *per capita* gain of 93 rupees in income

Some 30 million persons were living in areas under DDT spraying in India in 1952 Here, then, is effective control which points to the approach of highly significant changes in the epidemiology of malaria Indeed, a nation-wide three-year DDT spraying project to protect eventually some 125 million persons is now in its early stages This National Malaria Control Programme has been set up as a co-operative project which is supported not only by the Federal and State Governments but also by the Point Four Indo-American Aid Programme of the Foreign Operations Administration It involves residual spraying, treatment, and training, as well as construction of a DDT manufacturing plant Total expenditures over three years are expected to be some 14 62 crores of rupees ($30 million) Overall direction will be under the Ministry of Health of the

Government of India, through the Director of the Malaria Institute

Thailand

In 1949 the World Health Organization and the United Nations International Children's Emergency Fund set up a trial malaria-control demonstration project in Chiengmai, northern Thailand By 1951, some 550,000 persons were being protected from malaria by this DDT residual spraying scheme, and there was also widespread distribution of chloroquine The results were so good that the Thai Government, under Drs Luang Ayurakit Kosol, Director of the Malaria Service, and Luang Bhayung Vejjasastr, Director-General of Public Health, started a project which included a population of nearly 3 million in 1953 and will embrace some 5 million by 1956 In one area, consisting of seven villages, the malaria morbidity figure dropped from 50 5 per 1,000 in 1949 to 6 5 in 1950, and 2 1 in 1951, while it was still 42 per 1,000 in 1951 in a comparable but untreated area Costs are averaging about 8 (U S) cents *per capita* of those protected

Other Areas

Similar pilot projects for malaria control by DDT residual spraying have had great success in certain areas of other Asian countries, as in Afghanistan and Indonesia In the latter country, some 1¼ million persons, of the 28 7 million estimated to live in malarious areas, are being protected in 1953 by residual spraying, truly a good start under difficult conditions There are also DDT spraying projects in Pakistan, Taiwan, the Philippines, Borneo, Iraq, and Iran In 1953 the W H O convened in Bangkok the First Asian Malaria Conference Nothing could more clearly emphasize the importance of the DDT era than the bold statement that this conference met to discuss plans that visualize the elimination of malaria as a public health problem in regions embracing a quarter of the world's population—no less than 590 millions of people, half of whom live in areas where they were subject to malarial fevers in 1930, but of whom

today over 47 millions are being protected from this disease Certainly the day is coming in the not distant future when Asia will cease to measure her malaria cases by the hundreds of millions as she has done over the centuries It is entirely reasonable to expect that malaria in several Asiatic countries will soon be a minor rather than major public health problem

Many other countries could be listed in this review, as for instance throughout the West Indies, Central and South America, in various parts of Europe and Africa, and in Madagascar But perhaps enough has been said to make it clear than an enormous amount of residual spraying with DDT, or similar organic residual toxicants, is going on throughout the world and is having excellent results Probably *more than 100 million persons previously exposed* each year to malaria are now being protected These DDT control projects are cheap, they require relatively small technical staffs, and they are adaptable to most climatic and social conditions and to practically all species of malaria vectors We know now that entire nations can be cleared of malaria by residual spraying at economically feasible costs within reasonable periods of time

United States

As recently as 1912–15 the U S Public Health Service in a survey of twelve southern states estimated that a million cases of malaria were occurring annually in a population group of 25 millions, with incidence rates as high as 40 9 per cent in the Mississippi delta But by 1940 there had been a marked decline In that year Faust and De Bakey reported an average malaria mortality rate of 3 02 per 100 000 in fourteen endemic states This rate had been above 10 in 1920 and again in 1923 and 1936 Boyd wrote that 'there is some suggestion that the lowest level of this recession, at least insofar as natural or spontaneous factors may have been operative, was reached as long as 10 years ago', i e about 1930 In other words, the advent of DDT found malaria still endemic in the United States Between 1930 and 1940 it had shown its power to re-invade areas from which it had apparently altogether receded

DDT had its first practical application for malaria control in the United States in 1945 when the Communicable Diseases Centre of the U S P H S , under the guidance of Dr J M Andrews and others, co-operating with certain state health departments, began a joint programme which by 1950 had applied some 6 million residual DDT sprayings Since 1947 the objective has been to eradicate malaria as an endemic disease in the continental United States, a goal first clearly visualized by L L Williams, Jr and which now appears to be near In 1948–9, during a twenty-one months' epidemiological study in the formerly highly malarious states of Alabama, Georgia, Mississippi, and South Carolina, the U S P H S found only fifty-nine cases of malaria that might have originated within the United States Even lower figures have been reported since Thus malaria is obviously approaching an end-point For this reason, the U S P H S in 1950 requested the National Malaria Society to formulate a definition of endemic malaria and obtained the following 'Malaria may be assumed to be no longer endemic in any given area when no primary indigenous case has occurred there for three years' The term 'primary indigenous' refers to the first appearance of parasites in the blood of an individual infected by natural mosquito transmission in the given area

The addition of DDT to other factors has upset what promised to become a prolonged condition of light malaria endemicity in the United States, with occasional areas or periods of increased incidence It now seems likely that within a few years malaria may be declared to be not endemic in North America north of the Mexican border Since there are effective and extensive anti-malaria projects in Mexico and south to Panama the day may not be long distant when the continent of North America will be free from malaria

13

MALARIA RECESSION

United States

WHEN discussing the discovery of cinchona, we noted that historians disagree as to whether or not malaria existed at all in the Americas prior to the time of Columbus Whichever view is correct, malaria was certainly prevalent in early colonial days in the area now constituting the continental United States How abundantly it prevailed is not entirely clear Blanton and others have minimized its importance But Duffy writes that, 'Directly and indirectly, malaria was one of the most fatal of colonial diseases and shares with dysentery first place among the colonial infections ' However, malaria appears to have been rather slow in rising to major proportions The gametocyte seeds were brought in ever increasing numbers from Europe, the Caribbean, and Africa by settlers, traders, and slaves No doubt the vector anophelines were rather widely distributed long before human colonizing began But not until man began to improve conditions for the mosquito, especially for *A quadrimaculatus*, did malaria really become widespread Tendencies to push out into the wilderness, to settle near streams, to build small dams for water-power, to block natural drainage, all contributed to heighten the vector density during the eighteenth century so that malaria became widespread

That the United States was highly malarious throughout the nineteenth century seems clear, although there are few exact records to prove it In fact, the first complete mortality statistics on malaria in the United States were published as late as 1923 by Maxcy Ackerknecht noted,

During the 19th century, particularly under frontier conditions, there was no official and very little unofficial recording of diseases and to make things worse, just at its height malaria (or 'fever and ague', the

'chills', intermittent, remittent, bilious fever or whatever it was called) was so common that by many it was no longer regarded as a disease at all and therefore, of course, not recorded as such In the beginning the 'chills' were regarded as a necessary element of the inevitable 'acclimatization' and after having 'shakes' for years people got so used to it that they hardly paid attention to a little ague This is a classic example of how an objectively dangerous and burdensome bodily condition can subjectively, by social convention, even lose the character of a disease

Incidentally, one sees this same social phenomenon in parts of Asia and Africa today

Another difficulty in determining the amount of malaria in past centuries stems from differences in the old and the modern nomenclature and clinical description of disease But when all the evidence is weighed, no one questions that malaria was highly prevalent in the south-east, in the upper and lower Mississippi Valley, eastern Texas, and in parts of California Mild endemicity extended northward into New England and also into the Columbia River Valley Oliver Wendell Holmes, in 1836–7, prepared a scholarly essay on the subject of intermittent fevers in New England, where the disease was held in check by the climate Holmes quoted Hubbard's *History of New England* (1815) as noting that 'the salubriousnesse of the aire in this country depends much upon the winter's frost' Certainly, the three or four months warm enough in the north for incubation of the parasite in the mosquito were much less conducive to the development of solid endemicity of falciparum and vivax malaria than the eight- to ten-month season in the south

Among many incidents, Holmes, in his essay, *Apostle to the Indians*, told of the famous John Eliot suffering so much from malaria that he had said, 'Had our Blessed Jesus at any time sent His waggoner to fetch this old Jacob away, he would have gone without the least Reluctancies' Hubbard added, 'Labouring once under a Fever and Ague, a Visitant asked Eliot, How he did? And he reply'd, Very well, but anon, I expect a Paroxism'

Much important testimony as to the prevalence of malaria in the Mississippi Valley is found in the writings of Daniel

Drake, especially in his monumental work on the diseases of the *Interior Valley of North America*, the first volume of which was published in 1850 and the second in 1854, two years after his death He had travelled over 30,000 miles to make the surveys he thought essential to obtain material for his reports Osler called Drake, 'In many ways the most unique figure in the history of American Medicine', and Garrison said of Drake's treatise, 'There was nothing like this book in literature, unless it be Hippocrates on Airs, Waters and Places, and even Hippocrates made no attempt to map out or triangulate the geographic locale of disease ' Certainly Drake's observations emphasized the prevalence of malaria in the United States in his time

Why malaria has retreated so completely from the United States is a question that has aroused much speculation, especially since there appear to have been no significant changes in the invasive properties of the parasite, vectorial powers of the insect, or immune defences of the population Americans overseas readily become infected, paretics and volunteers at home can be inoculated easily with local strains of plasmodia by local anopheline mosquitoes, and the latter will also readily transmit exotic strains

Malaria in the United States in the past has probably been transmitted by four members of the *maculipennis* complex These four were once considered to be a single species, called *quadrimaculatus* The latter name is now restricted to that species that has been distributed principally over the eastern half of the country Here it has been particularly well adapted to the warm standing waters of the coastal plains *Anopheles occidentalis* and *freeborni* are the Pacific Coast representatives of the complex, and the fourth species is *A earlei* which prefers northern breeding places in the east Of these four species, *occidentalis* and *earlei* were easily deviated to animals and apparently ceased to have any importance as vectors of malaria as soon as frontier conditions gave way to land cultivation and animal husbandry

The Californian species—*A freeborni* no doubt was the vector of 'miner's fever' in early days and it has been responsible for a fair amount of malaria in the Central

Valley But it was restricted in distribution by the long, dry, and hot summers Moreover, it often fed on animal blood So, even when irrigation greatly increased its density, the resulting malaria was limited to one or two districts in California During 1910–12 malaria practically disappeared following a modest degree of irrigation regulation and certain minor anti-mosquito operations Despite enormous increases in the density of *freeborni* due to rice culture since 1912, there has been no mass reappearance of malaria although occasional sporadic attacks occur In 1952, for example, there were thirty-four local cases traced to the fact that a malarious Marine from Korea had slept out of doors four nights and had thus infected some *A freeborni* mosquitoes, which have not lost their ability to nurture malaria parasites

As regards *A quadrimaculatus*, presumably there has been an overall reduction in numbers since 1875 This would naturally follow as a result of the vast amount of land improvement for purposes of agriculture and real estate, as well as the extensive planned anti-mosquito drainage since 1915 Agricultural drainage in the United States has been a more effective anti-malaria measure than it has in Italy largely because the American vector *A quadrimaculatus* has a strong preference for standing water and is not apt to proliferate in drainage ditches as does *A labranchiae* of Italy

There were some anti-malaria mosquito-control projects in the States as long ago as the turn of the century For example, Dr Alvah H Doty, Port Health Officer New York, found one section of Staten Island in 1901 to have a malaria rate of 20 per cent He discovered that the problem was twofold, first the breeding of pest mosquitoes in a salt marsh, and second the presence of *Anopheles* mosquitoes in collections of fresh water One evening Dr Doty himself caught twenty-two mosquitoes—more than half anophelines—in a house opposite one in which he had found a case of malaria H M Biggs, the New York City Health Officer, called a malaria control conference (1901) and this group suggested a programme of (1) screening of beds and houses in the malarious areas, (2) confining malaria patients under

FIG. 16 A. Frontispiece of an early text by Bauderon

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screens, (3) treating cases with quinine, (4) eliminating mosquito breeding places by drainage and filling, (5) using larvicidal oil and larvivorous minnows Doty thereupon carried out a fairly large-scale anti-mosquito campaign, perhaps the first of its kind in the United States following the discoveries of Ross and the Italians

In 1899–1900 hundreds of Italians were employed in the construction of the Clinton Dam for the Boston and Eastern Massachusetts Metropolitan Water System At the same time many soldiers were returning from Cuba and Puerto Rico These two groups seeded Massachusetts, and other areas, with gametocytes to which, for some ten years, malaria in Massachusetts was largely traceable The increased incidence stimulated a control project in 1902–3 which involved filling, draining, oiling, and the use of minnows Other early mosquito control projects were carried out in California, in 1910, and in Long Island and New Jersey, about the same time

Abroad, the most notable anti-*anopheles* projects had been in Malaya, by Watson, and in Cuba and the Panama Canal Zone by Gorgas and his colleagues The latter, in particular, had wide publicity but the vastness of the Canal project caused many in the United States to believe that malaria control by anti-mosquito measures was too costly for an average community At any rate not much control was attempted for fifteen years after Ross's discoveries Then, in 1913 and 1914, as described in a later section, the United States Public Health Service supervised demonstrations of malaria reduction by anti-mosquito methods in Roanoke Rapids, North Carolina, and Electric Mills, Mississippi

During the First World War the U S Army in cantonment areas and the U S Public Health Service outside the military camps carried out no fewer than forty-three anti-mosquito projects in fifteen states, protecting 1¾ million civilians and over 800,000 military personnel Many towns and villages which had benefited by this programme continued the control measures at their own expense after the war

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FIG 16 B Title page of an early text by Bauderon

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During 1920–2 the U S P H S, with The Rockefeller Foundation co-operating, carried out a programme of 'Co-operative Malaria Control Demonstrations' in order to popularize malaria control work and to form nuclei around which state health departments could build up malaria control programmes Some forty towns in eleven southern states participated and successfully provided malaria protection to over 300,000 persons at annual *per capita* costs of about 81 cents These demonstrations marked the beginning of malaria control by state health departments and provided a strong impetus throughout the south-east Then from 1933 to 1935, during the depression, when many factors had combined to promote endemic and even epidemic malaria, the Civil Works Administration, Emergency Relief Administration, and Works Progress Administration, supervised by the Public Health Service, carried out many anti-malaria and anti-mosquito projects It is estimated that these agencies constructed 32,000 miles of average-size ditches, draining 623,000 acres of land, a definite anti-malaria factor in spite of inevitable defects in planning and operation

During the Second World War, again the Army in its cantonments and the Health Service in extra-cantonment areas, co-operating with state agencies, carried out no fewer than 2,200 mosquito-control projects in 19 different states Over 20,000 miles of ditches were cleaned or newly dug, and over 660,000 acres of mosquito breeding places were treated with Paris green or oil The areas involved were protected almost completely and the programme undoubtedly had a suppressing effect on malaria One should also note the extensive Tennessee Valley programme and the many well-directed routine state and county mosquito-control projects which have involved the expenditure of large sums for anti-malaria measures Finally, since 1945, as already mentioned, there has been the widespread use of DDT and other residual sprays To doubt that 'vector reduction' has been one factor in the decline of malaria in the United States seems unreasonable even if in some areas, formerly malarious but now free of the disease, the density of the vector anopheline is as high or even higher than ever

Probably many factors have been involved in the recession of malaria in the United States For example, one recognizes substantial economic advances in the South These have brought about much greater use of screening and of household insecticides such as pyrethrum spraying Since 1930 hardly a house in the formerly malarious area has been without its 'flit-gun' There has been notable improvement in quality and quantity of anti-malaria medication, and more frequent use of doctors Quinine, which was \$4 or more per ounce in the Civil War period, dropped in price to about 25 cents in 1913 and not long thereafter Bass's 'standard treatment' widely displaced the less effective 'chill tonics' There has been a tremendous amount of anti-malaria and agricultural drainage Le Prince in 1927 estimated that some 450 millions of dollars had been spent on farm drainage, and no less than 110,000 miles of open ditches, and 45,000 miles of tile drainage constructed There has been a disappearance of mill-ponds and wide control of impounded waters Finally, one notes vastly improved general and public health education, and a considerably expanded animal husbandry The latter, with its large increase in cattle-breeding, has resulted in more frequent deviation of the vector *A quadrimaculatus* from man to animal for its blood meals

A vast population shift has occurred in which tremendous numbers of gametocyte carriers have left the malarious areas of the South and moved into northern cities where their parasites have by now mostly died out, harmlessly An acceleration of urbanization in the South has taken large numbers of people into better-protected areas away from malariogenic waters River and stream training has been an important factor and has included not only small projects but such tremendous schemes as that of the Tennessee Valley Authority which has greatly reduced malaria in certain areas of five states In the old days, river travel and river settlements in the South were constant sources of malaria but neither one is any longer significant Finally, the climate of much of the United States has never in modern times been ideal for the perpetuation of malaria

Development of the malaria parasite within a mosquito ceases when the average temperature falls below 60° F. If vectors and gametocytes are abundant this climatic handicap is hidden, but once the necessary 'surcharge' is lacking, the retarding effect of the colder months makes itself evident.

The above-mentioned factors have brought about not only a great overall reduction in contact between man and malaria vector in the United States but also a depletion of the gametocyte reservoir, which is now almost dry. These two elements—vector and gametocyte—are the keys to the 'mystery' of malaria recession. There is a critical density level for each species of malaria vector. When the incidence of the vector mosquito falls below this critical number in a locality, malaria transmission tapers off or ceases entirely. After a relatively short period of such curtailed or suspended transmission, the incidence of gametocyte carriers naturally falls. Gametocytes, just as surely as anopheline vectors, have a critical density in any locality. If there are too few gametocyte carriers in a community there will be no significant malaria transmission. Gametocytes must remain above a certain level if a sufficient number of mosquitoes to propagate malaria are to be infected. The critical density of neither the vector mosquito nor the gametocyte is fixed or independent. Each depends to a considerable extent on the other, in inverse ratio. But there exists in each case a minimum level below which malaria transmission is unlikely, regardless of the magnitude of the other factor.

Once these two factors have concurrently fallen below their respective average critical density levels, the malaria transmission rate falls precipitously. After a time, it is quite possible for one of the factors to rise considerably above the old critical level without initiating renewed malaria transmission. However, if both factors rise above their critical levels concurrently, then malaria transmission will certainly occur, unless some preventive measure promptly blocks the operation of this phenomenon.

So with reduction of vector mosquitoes and of gametocytes going on concurrently in the United States, a notable recession of malaria has occurred.

The fact that malaria incidence in the United States began to decline before there were anti-malaria projects based on a knowledge of transmission should not be allowed to hide the importance of conscious measures of control during the twentieth century The word 'natural' applied to the disappearance of malaria from the United States may be misleading The agricultural, economic, physical, and social changes have been mostly man-made In this atomic age, many of these changes could be suddenly reversed Then there might follow a 'natural' reappearance of endemic and even epidemic malaria

We conclude that the regression of malaria in the United States has been due to no single cause but rather to many interlocking factors Among these one should recognize and not underestimate the effect of conscious efforts at malaria control since 1916 Dr Hackett has pointed out that even if malaria in time might have disappeared from the southern United States through 'natural' causes, yet by then it would certainly have cost the nation more than the money spent in the last decade to accelerate its departure

One should not assume that it is today a waste of funds to continue some planned malaria-control measures, in a country now relatively malaria-free—like the United States Experience thus far in areas formerly heavily infested gives no adequate basis for such an assumption However, there can safely be a lessening of direct malaria control effort For instance, it may become possible to suspend periodically the use of insecticides for one or two years at a time, as successfully practised in Greece This requires careful experimental testing on an ever-widening basis The cost of malaria control may thus safely be reduced in areas from which the disease has apparently disappeared Such interruption in the use of organic toxicants might also help to avoid development of insect resistance, common in house-flies and now appearing in anophelines

Europe

Malaria was fairly widespread in Finland, Sweden, and Denmark in the nineteenth century Indeed, there were

severe epidemics with as many as 40,000 cases in Finland in certain years Malaria regression in Finland dates from about 1900 although there were over 1,200 cases in 1945 after the war The epidemic started in 1941, Russian soldiers having introduced the parasite In Sweden the decline dates from about 1860, although there were a few cases in the latter country in 1939 Malaria cases in Denmark in 1875 totalled 5,331, in 1885, 2,273, in 1900, 275, and in 1920, 15 The decline was thought to be due to better housing, more quinine, a considerable amount of drainage, and increased deviation of the vector mosquito to animals for its blood meals

Malaria was much more prevalent in Germany prior to 1850 and had regressed fairly steadily from that time until the Second World War when the incidence increased temporarily

In France the marshy regions between the estuaries Charente and Seudre and extending from the sea to a line running south from Rochefort to Saujon, used to be very malarious and still produce occasional indigenous cases Alsace was malarious up to about 1885 but the disease has since practically disappeared and it did not reappear during or after the Second World War

England also had a good deal of malaria up to about 1850 For centuries malaria was entrenched in the Fen country, the marshes of the Thames Estuary, the marshes of south-east Kent, the low-lying country around Bridgwater in Somerset, and the Ribble district in Lancashire The marshes around London were so prominent a feature of the landscape that Cromwell was often called 'King of the Marshes' As Sir William MacArthur has pointed out, these low-lying areas were notorious for ague Sydenham described the autumnal intermittents as being particularly severe in England in 1661–4 It is interesting that malaria in Virginia in the seventeenth century was often called 'the Kentish disorder'

MacArthur notes that when Defoe visited the Essex marshes in 1722, he was told that local men went to the uplands for their wives but the latter often succumbed to

ague soon after going into the marshes Defoe said it was frequent to meet men who had had five or six to fourteen wives, 'nay, and some more!'

Brotherston notes that malaria was prevalent in Scotland during most of the eighteenth century, especially in the lowlands and midlands, sometimes seriously hindering farming operations It disappeared rather suddenly about the beginning of the nineteenth century, due, Brotherston believes, partly to agricultural drainage and partly to increased numbers of cattle and their greater survival rate following improved methods of feeding

Interestingly, the distribution of malaria in England in 1919 following the First World War appears to have been almost identical with that in 1860 Much less malaria followed the Second World War and in neither case was the 'concentration of contagion', i e the density of gametocytes, sufficient to maintain an endemic focus for more than a few years

The reasons for the regression of malaria in England and Europe are probably in part the same as those responsible for its retreat in the United States No doubt the increasing availability and lower cost of quinine has been one factor Soil drainage and river training probably also had a strong influence The habits of the non carrier *A typicus* are such that it is adapted to cultivated lands Its larvae are found in small, shallow breeding places, often artificial, with scanty vegetation and subject to major temperature changes Hence, this species, which fortunately prefers animal blood meals, is probably more abundant than ever But the vector *A messeae*, in its aquatic stages, typically occurs in large, densely overgrown breeding places, the depths of which *prevent extreme changes of temperature* Increased soil cultivation and river training have tended to eliminate such places and have thus very likely reduced the incidence of *messeae*

There has also been a dissociation between the fresh-water species of the *maculipennis* complex and man, mainly following improvements in agronomy Senior White believes, for instance, that the introduction of turnip culture

in England in the mid-nineteenth century in order to provide winter food for cattle, saved the herds from annual slaughter and thus greatly increased deviation of mosquito from man to animal. Finally, it is likely that progressive heightening of social, economic, educational, medical, and public health levels, with improved domestic hygiene, must also be taken into account.

As Hackett points out, when, in the early 1930's, the *maculipennis* complex in Europe was resolved into its constituent species by Missiroli and colleagues, it was found that only *A. atroparvus* was able to support a mild endemic malaria in the low-lying belt of land that had gradually been reclaimed from the ocean along the North Sea coast, partly in the Netherlands and partly in Germany. This species still maintains some endemic malaria in a few areas of east Friesland (Germany), north Holland, Spain, Portugal, and the Black Sea.

However, in Europe as in the United States, there has no doubt been an interplay of many factors, not the least of which has been a lowering of the incidence of the vector and a lessening of its contact with man, in climates not ideal for malaria in the first place. Also, it seems likely that *messeae* has never been a really dangerous vector, for this species never seems to be so strongly attracted to man as are *atroparvus* and *labranchiae*. Some potentiality for malaria no doubt remains wherever the disease was once known. But only in such disturbances as war and major economic depressions can malaria now regain any of the ground it has lost. Modern technique and drugs for dealing with this disease sharply limit the dangers of any serious resurgence due to natural cyclic tendencies.

The story of malaria regression from Europe and the United States illustrates, among other things, the importance of environmental changes that lessen the incidence of vector breeding places and the degree of contact between the insect and man. In countries where malaria control is recent and consists entirely of residual spraying it would be wise not to overlook the non-chemical factors. Environmental sanitation and improvement of domestic *hygiene*

should be practised to the fullest extent finances will permit In addition to the obvious benefits such measures would bring, it seems likely that much money might be saved by periodic curtailment of the use of insecticides, without fear that malaria would recur as a public health problem

War Heightens Malaria Endemicity

War nearly always intensifies malaria of whatever endemicity and sometimes it transforms potential into actual endemicity Many phases of a state of war tend to promote malaria transmission Not infrequently the numbers of vector mosquitoes and of human carriers are simultaneously increased and this results in malaria epidemics

For example, there is often a breakdown in administration of health department activities malaria control services, distribution of anti-malarials for treatment and prophylaxis, medical treatment in hospitals, dispensaries, and homes all are curtailed, disrupted, or entirely stopped for lack of authority, funds, materials personnel, transport, or because of local fighting or the fear of it

Then there is the factor of disruption of the community Normal facilities, including food and clothing supplies, are reduced or unavailable People may be forced to live precariously in partially destroyed houses, or farm buildings, or in open fields, forests, or caves through fear or because of actual warfare or war damage There may be over-population of endemic areas, movement of non immunes into malarious areas or of gametocyte carriers into potentially endemic areas The mass movement of civilians or troops, the transfer of workmen, the formation of guerrilla settlements, the repatriation of displaced persons, the return of war prisoners, the demobilizing of malarious soldiers—all are factors which may contribute greatly to increased malaria incidence The killing or removal of livestock and the destruction of stables may tend to force zoophilic species to feed more often on man The stabling of military animals in the middle of a village may attract unusual numbers of a vector species

Finally, there is often the creation of breeding places for vector mosquitoes. There may be the opening up of jungle areas; diverting of streams; abandoning of open mining works; damage to sewage, water pipes, dikes, irrigation and drainage systems; shell, bomb, and mine craters; trenches; fox-holes; tank traps; vehicle ruts; increased number of stagnant pools; the damming of streams by rubble from demolished embankments, bridges, and buildings; the blocking of drainage by hastily built airfields, highways, causeways, and assorted military installations. All these and still other factors may operate to increase malaria endemicity.

On the other hand, in some cases the effective measures taken by military authorities and the aid given by them to local communities may tend to reduce the incidence of malaria in communities. But throughout all history war generally increased the incidence of malaria and this was true of the First and Second World Wars.

14

INSECT RESISTANCE TO TOXICANTS

MAN is at war with insects that affect his food-supply, his shelter, and the health of himself and his domestic animals It has not been sufficient protection merely to change the environment by clearing, drying, cultivating, and by erecting habitations Such balances as are thus established are precarious and easily upset So man has turned to insecticidal chemistry for help and has developed sprays and powders that have been used more or less intelligently for many years Chemical weapons must be selective, they must destroy insect enemies and not those insects, birds, fishes, and mammals that are helpful to man's economy The killing of beneficial insects, parasitic on harmful species, has been a special hazard in the use of insecticides

One aspect of the use of chemicals to kill insects is now becoming especially important It is the problem of resistance to insecticides This resistance is not something that develops in a given insect during its lifetime for the susceptible insects die It is an inherited character There are individual insects that have an unusual margin of resistance due to certain genetic characters Gradually a resistant race of insects is produced by a mass-selection phenomenon The insecticide kills off the susceptible individuals, leaving a small percentage of resistant insects which then breed true Another and secondary consideration is sometimes the fact that these resistant insects normally would be eliminated or kept down to small numbers by parasites and predators or other environmental factors But when the chemical treatment destroys their natural enemies they survive and a resistant strain of the species is developed, the speed and extent of the build-up depending on how far the heterozygous genes can accumulate to produce resistant genotypes Man may thus assist in the evolution of insect strains that are dangerous to his own existence

At a symposium of the World Health Organization the following definition of the word *resistance* in relation to insects subjected to toxicants was agreed upon for use in the discussions 'Resistance to insecticides is the development of an ability in a strain of an insect to tolerate doses of toxicants which would prove harmful to the majority of individuals of a normal population of the same species The term 'behaviouristic resistance' describes the ability to avoid a dose which would prove harmful'

Hess previously had described three types of true resistance

1 *Physiological* the ability through biochemical processes to withstand a toxicant after it has entered the body
2 *Morphological* the ability through morphological structures to prevent a toxicant from entering the body
3 *Behaviouristic* the ability through protective habits or behaviour to avoid injurious contact with a toxicant

There is also a non-inherited *tolerance* sometimes developed in individuals by a succession of sub-lethal doses, as in a man who gradually becomes immune to increasing quantities of arsenic This phenomenon is not troublesome as a rule in the control of insects

That insects can become resistant to insecticides has been evident for some time As long ago as 1887 John B Smith, of the New Jersey Agricultural Experiment Station, observed that the San José scale insect in California became resistant to kerosene The possibility of growing resistance to insecticides was first pointed out by A L Melander in 1914, also in connexion with San José scale This was confirmed by H J Quayle, who in 1916 demonstrated that the red scale insect showed marked resistance to fumigation with hydrocyanic acid gas In 1928 strains of the codling moth were found to resist poisoning by arsenicals Today strains of house-flies, mosquitoes, lice, and certain other insects have begun to show troublesome resistance to the newer organic toxicants such as DDT

In Italy, for example, extensive use of DDT was begun by the Allied Forces in 1944 and has been continued ever since in certain areas In 1947 Giuseppe Sacca and Ezio Mosna, in Missiroli's laboratory at the *Instituto Superiore di Sanità* in Rome, observed in the Pontina that, respectively, house flies and a strain of *Culex* mosquito had become resistant to DDT These were the first recognized occurrences of fly and mosquito resistance to DDT The same year Wiesmann reported resistant house-flies from Sweden in an area north of Stockholm in which DDT had not been used Here was a strain in which most of the individuals were naturally resistant to DDT, in contrast to the Italian strain in which at first most of the individuals were susceptible In fact, so few were naturally resistant that they were not noticed during the first spraying Only when the susceptibles had been killed off did the resistant strain build up to noticeable proportions

Today house-flies in many countries have become resistant to DDT and often to several other organic toxicants such as benzene hexachloride, chlordane, and dieldrin Some strains of house-fly can now withstand doses of DDT a thousand times stronger than the lethal dose for susceptible flies

Several species of *Culex* and *Aedes* mosquitoes, including, for example, *Culex pipiens*, *quinquefasciatus*, and *tarsalis*, *Aedes dorsalis*, *nigromaculis*, *sollicitans*, *taeniorhynchus*, and others are now known to be resistant to DDT and in some cases to other insecticides Various species of lice, fleas, sandflies, cockroaches, and bed-bugs have also developed resistance to DDT No other insect than the house-fly has yet become resistant to more than eight times the lethal dose for susceptible strains

The situation as regards malaria-carrying *Anopheles* has developed slowly but is now causing apprehension For example, in Panama, Trapido has reported that in some areas *A albimanus* shows behaviouristic changes developed apparently as the result of some years of intensive DDT residual spraying Whereas at first this mosquito would rest on DDT-treated surfaces and so take up lethal doses,

it now tends to avoid the insecticide and thus to escape death from DDT poisoning In Greece, Professor G A Livadas has reported that *A sacharovi* (sometimes called *A elutus*), after six years of DDT residual spraying, and several of DDT larviciding, is now showing a high survival-rate after contact with DDT, both in the field and in the laboratory This is in sharp contrast to the original *findings in the same area There also appears to be a similar* resistance to benzene hexachloride, although the latter insecticide has never been used in the area In Java *A sundaicus* has become strongly resistant to DDT in one area

Sometimes it has been found that one species is able to withstand greater doses of DDT than can another species In Sardinia, for example, Trapido found that *A claviger* has a higher lethal dose than other species Yet in Sardinia there is no evidence of increased resistance of any local anopheline after six years of intense exposure to DDT On the other hand, house-flies in the same area have become thoroughly resistant to all of the residual toxicant sprays

Nowhere in the world prior to 1953 had anophelines developed a resistance to organic toxicants sufficient to make *malaria control by DDT residual spraying impossible* But recent evidence shows that the species *sacharovi* in Greece and Lebanon and *sundaicus* in Java have now reached this point

Obviously, it behoves man to

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SOME INTERNATIONAL ASPECTS OF MALARIOLOGY

DISEASE is thoroughly international, a fact well illustrated by malaria Insect vectors have no political tropisms, plasmodia have been crossing boundaries for centuries, and neither have been much hampered by customs and immigration officials More frequent airplane transport and heightened intercourse with the tropics in modern times have accelerated an intercontinental exchange of parasites and mosquitoes To an ever greater extent disease and its control in one country have practical significance in other countries

Even as disease has international characteristics, so has the practice of medicine, increasingly since ancient days when Greek physicians went to Rome Such overseas journeys at first were largely for financial gain But by the time of the Renaissance other motives were evident Paracelsus, for example, frequently expounded the educational advantages of studying disease in foreign countries and he practised what he preached When accused of being a man without a home (how many malariologists have been similarly taunted!), Paracelsus, in the fourth of his famous *Defensiones*, as quoted by Sigerist, replied, 'Diseases wander hither and thither throughout the breadth of the world, and stay not in one place If a man wish to recognize many diseases, let him *travel if he travel far, his experience will* be great and he will learn to recognize many things ' He continued, 'How can a good Cosmographus grow in the chimney corner, or a Geographus?' Then he added that the physician 'should be a Cosmographus not to describe how the countries wear their trousers, but to attack more bravely what diseases they have'

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development of colonies by Spain, Portugal, England, and Holland led to a wider interest in foreign diseases, particularly in the tropics France, Germany, and the United States reacted similarly at later dates Research institutes and laboratories for the study of exotic diseases, usually with prime interest in malaria, were an early aspect of colonial expansion

But the experimental study and practical control of communicable diseases within the borders of one country by nationals of another country or by representatives of international voluntary or official organizations, constitute with rare exceptions, phenomena of the twentieth century There have been occasional international health consultants in the past, as, for example, Peter Frank (1745–1821), who went all over Europe as adviser to governments and kings on matters of sanitary procedure As Barkhuus has said, Frank was almost 'an international institution in himself' But until the formation of the Pan-American Sanitary Bureau in 1902, international public health was chiefly a matter of sanitary conventions, the terms of which were to be carried out in each country by its own personnel

Nevertheless, many of the fundamental facts and techniques of malariology have been established by doctors, engineers, entomologists, and other scientists at work in places far from their homes, 'from the Bight of Benin to Bengal and beyond' One recalls the achievements of Laveran in Algeria, Ross and Christophers in India, Gorgas and Le Prince in Panama, Watson in Malaya, Schuffner and Swellengrebel in Indonesia, Rodhain in the Belgian Congo, and many others Some of the story has already been told in previous chapters, but it may be of interest to give brief accounts of a few of the organizations and men involved in the development of what may perhaps properly be called *international* or *overseas malariology*

Unfortunately, it is not feasible at this time to present as many aspects of overseas malariology as we believe should be included under the title of the section Brief accounts of certain malaria-control activities of some multi- and bilateral international agencies have been included But the story of

the achievements of specialized schools of tropical medicine, such as those in Liverpool and London, Amsterdam, Hamburg, Calcutta, and elsewhere, have perforce been omitted Nor can we recount the exciting history of malaria investigation and control by British, Dutch, Belgian, French, Portuguese, American, and other nationals in overseas research councils, health departments, hospitals, universities, and research institutes Suitable recognition of all the many individuals and organizations that have added such a striking international flavour to malariology cannot be given here But enough material will be presented to illustrate progress and potentialities in the field of joint action among nations for the attainment and maintenance of community welfare and peace

Such progress, however limited, is welcome because most of us are apprehensive and uncertain over the immediate future and what we can do about it A majority of mankind still cherishes political and cultural barriers and continues to live by ancient behaviour patterns The doctrine of competitive survival predominates over the desire for unity and for international welfare It is the hare of self-interest versus the tortoise of co-operative endeavour

International preventive medicine has even greater importance today than ever before The physical condition of hundreds of millions of people, hungry for food, land, and security, makes them eager for that relief from the ravages of disease that the modern practice of malaria control and general public health can afford The problems of society are complex and confusing, but thirty years of international experience have emphasized one point political afflatus and free 'hand-outs' are not logical measures for raising debilitated, parasite-beaten communities to significantly higher agricultural, economic, or social planes Dollars and DDT are not enough! On the other hand, great progress in the development of bet [illegible] policies, and more [illegible] in a community th [illegible] chronic malnourishment, paludism, and parasite infestation by modern public health procedure Malaria control, for

example, often has a strong and persuasive impact on the neediest—the lowest echelons of society, least impressed by abstract concepts.

Sound public health practice comes to underdeveloped areas only by patient training of public health personnel and by building reasonably well-organized national and local public health departments—by technical aid and practical co-operation rather than by charity. Spectacular gifts of materials, dozens of overnight experts, however well intentioned, seldom have much effect in developing public health improvement and may engender ill will. Incidentally, this pitfall in the practice of preventive medicine is being avoided with increasing determination and success by international health organizations at the present time.

Sir John Simon in 1890 in his monumental work, *English Sanitary Institutions*, wrote of our planet gliding 'by successive yearly rounds towards her last haven, whether of darkness or of light'. He noted that in man, this planet's 'paramount creature', the 'beast of prey is not yet all extinct'. However, man's 'organs of higher life are in growth', and he continues to rise toward what Sir John called 'the religion of mutual helpfulness'. Verily, such international public health practice as 'overseas malariology' is a vital part of a 'religion of mutual helpfulness'.

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MULTILATERAL EFFORTS

IN the history of international efforts to control malaria there have been three organizations operating along multilateral lines that have made outstanding contributions Unfortunately, only brief accounts can be given of the malaria work of these bodies—the Pan-American Sanitary Bureau (P A S B), the Health Organization of the League of Nations (H O), and the World Health Organization of the United Nations (W H O) Special mention must also be made of assistance in malariology given by the United Nations Rehabilitation and Relief Administration (U N R R A) and by the United Nations Children's Fund (U N I C E F) The Colombo Plan and the Commission for Technical Co-operation in Africa South of the Sahara (C C T A) are also to be noted

The Pan-American Sanitary Bureau

The first modern international health agency that was empowered by treaty to operate within the borders of member nations was the Pan-American Sanitary Bureau This pioneer was established in 1901–2 in Mexico City at the second Inter-American Conference of American States Organizational principles were laid down by the First Pan-American Sanitary Conference in Washington in 1902 The Organization of American States had been founded in Washington in April 1890, at an International Conference and, although originally designed to collect and distribute commercial information, it now interests itself in a wide variety of matters of mutual concern

The P A S B is an agency of all twenty-one American Republics and, since 1924, has been regulated by Pan-American (or Inter-American) Sanitary Conferences Since 1947 the P A S B has served also as the Regional Office of the World Health Organization for the Western Hemisphere,

maintaining its own identity and certain separate functions and programmes

The opening of the Bureau in Washington, in December 1902, was a logical culmination of several international conferences and agreements among the American nations The duties of P A S B were outlined as follows (1) each member Republic was to furnish the Bureau with current data on the sanitary conditions of its ports and territories, (2) each government would aid the Bureau in investigating outbreaks of communicable disease within its borders, (3) each nation would develop the widest possible protection of public health so that preventable diseases might be eliminated and commerce between the Republics facilitated, (4) the Bureau was 'to encourage and aid or enforce in all proper ways the sanitation of seaports, including the sanitary improvement of harbours, sewage, drainage of the soil, paving, elimination of infection from buildings, and the destruction of mosquitoes and other vermin', (5) the Bureau would have an annual budget, to which all member governments would contribute

The second and fourth objectives listed above constituted a revolutionary departure in the history of public health They gave a measure of responsibility to an international body for health conditions *within* member countries Although the P A S B placed emphasis on protection of trade as a motive for international concern with public health, it laid the bases for international health programmes originating also in social and humanitarian considerations

The annual budget of the P A S B has grown from an initial $5,000 to some $2 million, and its basic activities have widened from defence to offence The yearly sums available for international public health work in the Americas, in which the Bureau shares technical responsibility with governments, have expanded to about $6 million, a sum representing the combined funds of P A S B and the W H O Regional allocation, U N /W H O Technical assistance, and U N I C E F moneys allocated for health programmes in the Region

Just as W H O has regionalized its operational structure,

so the P A S B has subdivided the Americas into six zones Zonal offices conduct field work and provide closer co-operation with local governments The first three directors of the P A S B were Surgeons General of the U S Public Health Service The present director is Dr F L Soper, formerly of The Rockefeller Foundation He serves in the dual capacity of P A S B director and of W H O Regional Director Soper is also a notable malariologist

Since 1907 the P A S B has been concerned with malaria because throughout its sphere of influence this disease has been an outstanding public health problem, with mortality rates as high as 432 per 100,000 in some areas and a morbidity rate sometimes equivalent to 75 per cent in certain communities [illegible]

p[illegible]

information about the disease, and generally attempting to stimulate anti-malaria projects and the training of personnel The *Boletín de la Oficina Sanitaria*, a monthly publication started in 1922, published many articles about malaria, its prevalence and control The disease was discussed at the Sanitary Conferences in 1938–40, and, there was set up a *Comisión Panamericana de Malaria* In 1944 this Malaria Committee consisted of Drs A Gabaldon, C A Alvarado, A S Ayrosa-Galvão, V A Sutter, L Vargas, and L L Williams, with M F Boyd and H Hanson as advisers Questions of mosquito taxonomy and behaviour, of survey techniques, and of drug administration for therapy and prophylaxis received much attention The incidence of the disease was reduced, but until recent years still remained high

Today the malaria situation is remarkably changed We have already mentioned malaria eradication projects that are proceeding so successfully in Venezuela, Brazil, and elsewhere in South America Now, due in large measure to the initiative of the P A S B there is being developed in Central America the most comprehensive insect control campaign of the Western Hemisphere The governments of six republics and the territory of British Honduras, embracing a population of about 9 million persons, have formed a united front to stamp out not only malaria but other

insect-borne diseases which for centuries have been serious causes of death and disability In this co-operative effort the P A S B has joined hands with W H O, U N I C E F, and the Institute of Inter-American Affairs to assist the local authorities in their joint project

As already noted in preceeding sections of these lectures, the newer chlorine-based residual insecticides, such as DDT, have made possible highly effective techniques for insect control and malaria eradication With the mass, house to house spraying and dusting of insecticides, the vectors of insect-borne diseases such as malaria, urban yellow fever, typhus, filariasis, and perhaps others, can be brought under control by a unified and an integrated campaign

In this Insect Control Programme in Central America, the various governments do not depend entirely on insecticides and supplies furnished by U N I C E F and W H O Technical Assistance funds To an ever-increasing extent, locally financed materials are being used Moreover, local personnel, after having had special training, are gradually taking over the technical guidance of their respective national programmes, or are helping in a neighbour's project

At the end of 1953 over 20 million persons in the tropical Americas and West Indies were living in areas having malaria-control projects assisted to some extent by the P A S B /W H O organization Work is proceeding at an ever-accelerating pace It promises eventually no less than the elimination of malaria as a public health problem in this region where it has previously been the most widespread and persistent of insect-borne diseases How Ross and Gorgas would have rejoiced and how satisfying it must be to Watson and Le Prince to see this tremendous extension of their efforts to control malaria by anti-mosquito measures!

Malaria Commission of the Health Organization of the League of Nations

The League of Nations, established in 1919, had its first Council meeting in January 1920, and first Assembly in the following November–December Its Covenant stated, among many other objectives, that Member States 'will endeavour

to take steps in matters of international concern for the prevention and control of disease' In pursuance of this pledge the League set up an Epidemics Commission in 1920 primarily to co-ordinate efforts being made to deal with typhus fever, in Poland, Russia, the Baltic States, and in Greece

The Epidemics Commission was the only health organ of the League until September 1921 when it was taken into and superseded by a Provisional Health Committee, established by the Second Assembly of the League This temporary body became the Health Organization of the League in 1923 and thereafter was made up of three parts—a Health Committee, an Advisory Health Council which consisted of the Permanent Committee of the Office International d'Hygiene Publique, and a Health Section The last-named was the executive body of the H O and was an integral part of the League of Nations Secretariat

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Malaria Commission of the Health Organization of the League of Nations

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Sfarcic of the Kingdom of Serbs, Croats, and Slovenes, Professor Ciuca of Roumania, Dr Roubashkin of the Ukraine, Professor Marcinowsky of Russia, Dr Anigstein of Poland, and Dr Labranca of Italy

The Malaria Commission was instructed to inquire into the incidence of malaria, to draw up plans for investigating its epidemiology, to consider world quinine requirements, and to make special studies of malaria in Albania, Greece, and Persia

The need for special studies may be surmised from the statement of the Malaria Sub-committee in February 1924 that the basis of prophylactic measures against malaria was quinine 'If permanent results were desired, a very complicated programme would have to be realized Local conditions would have to be improved, sanitary works undertaken, and medical assistance organized Only quinine, however, could give immediate results This was the first weapon' Such a statement, twenty-six years after the work of Ross in India, is surprising The demonstrations of malaria control by anti-mosquito measures in Havana, the Panama Canal Zone, Brazil, Palestine, Malaya, Indonesia, the southern United States, and elsewhere, and the universal failure to achieve comparable results with quinine had not inspired many sanitarians There were some notable exceptions For instance, in January of this same year, 1924, M E MacGregor had written in *The Lancet* that ' the foundation of economic and modern antimalaria campaigns lies in the adoption of direct and permanent measures against only the proved breeding places of the definitely incriminated vectors '

The Malaria Commission, however, considered the primary measures against malaria to be thorough treatment, tracking down cases, and spreading propaganda for the use of quinine It believed that there was insufficient knowledge regarding other anti-malaria measures to pass judgement on them, an opinion that the record seems to show was not quite adequate although it was applicable to certain localities

In May 1925 the Malaria Commission sent a mission to

Palestine and Syria to investigate malaria and its control The group consisted of Nocht, Ottolenghi, Swellengrebel, James, Anigstein, and, from the United States, S T Darling, also Dr Lothian and Mlle Besson from the Secretariat of the League

In Palestine it was noted that successful use was being made of available methods of malaria control, including anti-larval oiling and drainage, minor bonification, and use of quinine Local authorities had set up a Malaria Survey Unit and a Malaria Research Section The Malaria Commission reported that, 'Our visit to Palestine has shown us what can be done against malaria in the way of an anti-larval campaign (*a*) if the work is done thoroughly and systematically and after an exhaustive preliminary survey (*b*) if conditions are particularly favourable for dealing with larvae: (*c*) if sufficient money is available ' But there was a willingness to believe that a 'natural' decline in malaria had taken place and the report added, 'In Jerusalem alone does the probability that the work done is the cause of an apparently permanent reduction in malaria, approach almost to a certainty '

At a meeting of the Palestine Anti malaria Advisory Commission, held on 19 May, several members of the League's Malaria Commission addressed the gathering Nocht reported that in 1924 and 1925 members of the Commission had visited Yugoslavia, Greek Macedonia, Roumania, Bulgaria, Italy, and Russia He noted that the commonly accepted methods of control were (1) complete and prolonged treatment of all cases, (2) treatment of gametocyte carriers, and (3) propaganda for household use [illegible] ises, and [illegible] Only in [illegible] al measures, largely because of the cost and partly because water was often used for household purposes

All but Nocht and James went on to Syria, where a tragic automobile accident caused the deaths of Drs Darling and Lothian and Mlle Besson, a disaster that ended the tour and resulted in irreplaceable losses to the Commission and

to malariology Darling's brilliant studies in malaria epidemiology and pathology and in the biology of malaria vectors of Panama and the southern United States, had been of immense value as regards species identification and behaviour characters He had also helped to develop the measurement of malaria incidence, especially by spleen palpation

In 1926 James and P G Shute reported on 'The First Results of Laboratory Work on Malaria in England' These authors were developing new and important tools for the study of clinical malaria and its treatment They were working at a mental hospital where patients were available who would be benefited by paroxysms of malaria The patients were infected by mosquito inoculation so that their attacks closely resembled those naturally contracted Thus conclusions having wide application could be drawn regarding clinical course and treatment of malaria

James made a point that at least 95 per cent of potential malaria-carrying mosquitoes that emerge from pupae never succeed in transmitting malaria Only a few mosquitoes that happen to pass their lives in sheltered quarters are successful in germinating the parasite to the sporozoite stage Hence it seemed to James a great waste of effort to attempt to control malaria by measures directed against the breeding places of mosquitoes as a whole or even against those of a single species better attempt to get exact knowledge of those few individual mosquitoes that transmitted, then attack them directly James discounted the fact that on a practical basis, malaria control requires a margin of safety, not pinpoint attacks against individual mosquitoes or houses true today even with the most modern sprays

Although in 1926 tested anti-mosquito malaria-control measures were too costly for most rural tropical areas, yet excellent and economical malaria control was being accomplished elsewhere in many communities, both rural and urban, by anti-larval measures Somehow the Malaria Commission for many years tended to undervalue these successes A complication was the fact that in some areas of the Netherlands, studied by the Commission, land reclamation

obviously did not diminish anophelines but actually increased their density by providing additional ditch-breeding places for *A. atroparvus*. Also, in Italy *A. labranchiae* multiplied prolifically in drainage channels.

In 1927 the Commission published a report on 'Principles and Methods of Antimalarial Measures in Europe'. At the time, the seven members, eight experts, and seven correspondents of the Commission represented fifteen different countries, mostly in Europe but also including Brazil and India. On the Commission there was no representative from the United States and almost no one who had ever had much success in controlling malaria by anti-mosquito measures. But it was a notable group of experts in all other aspects of malariology. Members of the Commission toured widely and their inspections constituted 'the first occasion when the collective thought of malariologists of different countries and different schools of teaching and practice had been brought to bear on local malaria problems studied on the spot'.

The task assigned to the Commission was 'to ascertain what measures are most appropriate in countries where the cost of public health measures is an important consideration, and where, in consequence, the anti-malarial measures that can be taken are limited financially in accordance with the relative importance of the disease as compared with the importance of other diseases and conditions which affect the public health ...' The Commission commented that

When the discovery of the mosquito cycle of the parasite was made, it was almost universally believed that a single simple method had been put within our grasp capable of application in all malarious districts. Since then nearly three decades have passed and such a method is still to seek. For these reasons, the Commission is unanimously of opinion that the scientific study of malaria must be continuously pursued in the laboratory and the field. We desire particularly to bring this view to the notice of European Governments and to suggest that each of those Governments which has not already done so should establish a small central permanent organization of selected workers who would devote their whole time to malaria research.

Here was a reasonable suggestion that was eventually implemented in several countries

The need was stressed for preliminary examination to ascertain what method is best suited to local conditions also, after work had started, the desirability of finding out at frequent intervals the amount and character of existing malaria It was not wise, the Commission suggested, to employ all available methods but only one or two which could be brought above a standard referred to as 'minimal effective degree of perfection' The Commission said that the *direct* measures of malaria control consisted of killing the parasite—in man by quinine and in the mosquito by destroying infected insects in houses The *indirect* measure most important was that of general bonification, aimed at improving the economic and social conditions of the people. The anti-malaria factor, in the opinion of the Commission was the change in the conditions of the life of the people The Commission's recommendations were open to question, in the light of successful and economical malaria control by anti-larval measures in some countries and by practical combinations of methods in others

In June–July 1927 James and Swellengrebel represented the Malaria Commission on a study tour in the United States, a trip authorized for the entire Commission in 1925 but postponed several times and finally greatly reduced in scope Each of the participants issued a report, the two being widely divergent in certain important aspects Professor Swellengrebel stated that there had been a great reduction in malaria incidence in the United States, due he believed to such factors as drainage, especially for agricultural purposes, disappearance of mill ponds, screening, and the Bass standard treatment with quinine James, on the other hand, reported that the malaria recession had been due to 'natural' causes rather than to anti-malaria mosquito-control measures He was not at all impressed by the latter during his brief and, one must say, rather casual tour

Engineer Le Prince, of the U S Public Health Service, in a reply to James, circulated by the Malaria Commission, asked, 'Why did malaria prevalence remain high in many

large areas where no anti-malaria measures were initiated while it simultaneously disappeared where malaria measures were actively conducted?' Le Prince noted the millions of dollars spent on wire screening, the hundreds of millions spent on agricultural drainage, and the many areas where anti-mosquito projects were in progress. Le Prince concluded, 'There is no question but that agricultural drainage and mosquito control has in many instances and over large areas reduced the prevalence of *Anopheles quadrimaculatus* (the vector) as it has been checked many dozens of times by weekly inspections of the numerous usual daytime resting places of *A. quadrimaculatus* in many portions of 13 states.'

Le Prince's reply had been based on observations over some eleven years of continually expanding practical experiments with malaria control by anti-mosquito measures in the southern United States, as described in later chapters.

It is interesting to observe how consistently James was sceptical of anti-larval measures. Here was a great scientist who made original and brilliant studies on the malaria parasite in man and mosquito, on the behaviour characters of mosquitoes, and on the clinical course and treatment of malaria. But early in his career he had failed to control malaria by anti-larval measures at Mian Mir, an Army Cantonment in India, and this appears to have markedly conditioned his views. What a pity James is not here today to see how the method that he and others on the Commission believed to be so important, namely the killing of infected mosquitoes in houses, has blossomed into spectacularly successful nation-wide malaria eradication programmes of residual spraying.

In 1930 the Malaria Commission toured India. James was not with this group which, interestingly enough, noted among other points, its opinion that much more malaria control by anti-mosquito measures could be done in certain Indian cities, like Bombay.

At the Third International Congress of Malaria, held in Amsterdam in 1938, the work of the Malaria Commission from 1930 to 1938 was reviewed by Professor Edmond Sergent, third President of the Commission. The first

President, Dr Lutrario, had made reports at the First and Second Congresses in Rome and Algiers, 1925 and 1930 respectively The second President, Professor Bastianelli of Rome, would have made a report had the Third Congress been held in Madrid in 1935 as originally planned

Sergent noted that between 1930 and 1938, as in the preceding period, the Commission's activities were directed particularly towards (1) *Questions of a general character*, such as standardization of malaria terminology, losses due to malaria versus the cost of anti-malaria campaigns, planning and providing malariology courses, e g in Singapore, and the Darling prize for outstanding work in malariology (2) *Epidemiology*, including biological characters of *Anopheles*, malaria in deltas of the Danube, Ebro, Po, and Rhine, housing and malaria—pointing out the importance of 'malarial houses' and that infection is usually contracted inside houses, varieties of *A maculipennis*, studied in Siam, China, and Roumania, studies of *P malariae* (3) *Treatment and Drug Prophylaxis*, involving a special study of the secondary alkaloids of cinchona This resulted in a new standardized mixture of cinchona alkaloids, named by the Commission *totaquina*, a preparation cheaper than quinine but practically as effective There was also a study of synthetic drugs such as plasmoquine and atebrin, an important general report in 1937 on *The Treatment of Malaria*, studies of drug activity against various species, stages, and strains of plasmodia, investigations of drug toxicity, experiments with collective treatment of malaria-infested populations, evaluation of the relative merits of atebrin and cinchona preparations, leading to the conclusion that the latter were most suitable for collective treatment (4) *Measures Against Anopheles*, including a study of naturalistic measures and of insecticidal sprays to destroy adult mosquitoes (5) *Immunity and Premunition*

Professor Sergent's report, as issued by the Health Organization, consisted of 16 mimeographed pages It is of some interest that, in the 640-line report, 8 lines were required to cover the subject, 'Measures against Anopheles' while 230 lines were allotted to 'Treatment and Drug Prophylaxis'

In 1945 there was published a *Bibliography of the Technical Work of the Health Organization of the League of Nations 1920–1945* This lists some 285 publications issued by the Organization and relating to malaria On analysis it appears that there were 137 documents on the epidemiology of malaria, some referring to control measures being employed in various countries, 102 publications regarding drugs for treatment or prophylaxis, 27 dealing with *Anopheles* or anophelism, 8 on the subject of anti-larval measures, 7 discussing housing and malaria, and 4 immunity It seems fair to state that the Malaria Commission was primarily interested in epidemiology and drugs and that it devoted considerably less attention to anti-mosquito measures of malaria control

Nevertheless, the work of the Commission was of the greatest importance for several reasons In the first place, it developed a remarkable spirit of co-operation between governments in the exchange of information about malaria, in co-ordinated laboratory experiments, and particularly in the training of personnel for malariology Secondly, the work of the Commission greatly stimulated a better and wider use of cinchona alkaloids for treatment and prophylaxis Thirdly, the Commission did much to make clear how the local epidemiology of malaria varies from place to place Hence the emphasis on the need for basic surveys, studies of *Anopheles* behaviour, recognition of races of *maculipennis*, studies of the parasite in man and mosquito There can be no question that the Commission drew worldwide attention to problems of malaria and its control

The Health Organization of the League convened several important conferences, for example the Pan-African Health Conference at Johannesburg in 1935 and the Inter-governmental Conference of Far-Eastern Countries on Rural Hygiene at Bandoeng, Java, in 1937 At each of these meetings malaria investigation and prophylaxis had much attention At the Johannesburg Conference the reports of Park Ross on pyrethrum spraying were useful in calling attention to this effective measure The recommendations regarding malaria control adopted by the Bandoeng conference were

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widely distributed and were of considerable help to governments in the formulation of malaria policies All in all one would say of the work of the Malaria Commission of the League of Nations, that it was highly influential in stimulating governments to pay attention to malaria and its control Moreover, the Malaria Commission did much to develop international co-operation in the field of malariology

The last meeting of the Health Organization was in 1939 In 1946 its functions were transferred to the Interim Commission of the World Health Organization

United Nations Rehabilitation and Relief Administration

The Second World War destroyed the Health Organization of the League of Nations, as it did the League itself and so many other institutions of international value But it did not annihilate the idea or the ideals In the midst of bitter warfare, in November 1943, it was possible to bring together in Washington representatives of forty-four countries to sign an agreement establishing the United Nations Relief and Rehabilitation Administration, commonly called U N R R A Within a month's time U N R R A had established a Health Division, which in the following years carried out the largest international emergency medical operation ever known, with a staff of 1,363 personnel of many nationalities Under the direction of the late Dr W A Sawyer, with headquarters in Washington and regional offices in London, Shanghai, Sydney, and Cairo, the division supervised the spending of more than $168 million for health work and supplies

Criticism of welfare measures undertaken in war-time is easy Like all emergency and, therefore, hasty activity, U N R R A 's projects were often expensive and rarely could be shaped with much regard to long-range planning Money was spent quickly, and undoubtedly there was some of that great waste inherent in all aspects of war But the fact remains that the U N R R A Health Division bridged the gap which the Second World War caused in the evolution of international preventive medicine In addition to

FIG. [illegible] Spraying a DDT-oil formulation as a larvicide in Sardinia during the Anopheles Eradication Project known as ERLAAS, 1946–51.

Photograph by H. [illegible], used by courtesy of Dr J. [illegible] Logan, formerly director of ERLAAS

FIG 18 A WHO Malaria Control Project in Taiwan A member of Malaria Control Demonstration Team is spraying a farmhouse kitc with residual DDT

Courtesy of the Malaria Section WHO Geneva

alleviating great suffering, it fought typhus, typhoid fever, diphtheria, and malaria in Europe, cholera and plague in China, tuberculosis and malnutrition in many countries

The U N R R A Health Division took the initiative and contributed fundamentally in malaria-eradication programmes in Greece and Sardinia, co-operating in each case with the local government and, in the case of Sardinia, also with The Rockefeller Foundation These activities illustrate that the U N R R A Health Division implemented some projects that will long have a beneficial influence on public health According to the Rt Hon Philip Noel-Baker, U N R R A constituted 'the greatest act of charity the world has ever seen'

World Health Organization

At the United Nations Conference in San Francisco in 1945, the delegates of Brazil and China suggested that a meeting be held to set up an international health organization Therefore, the United Nations Economic and Social Council, soon after its establishment, officially called for such a gathering, to be organized by a Technical Preparation Committee which met in Paris in March April 1946 The resulting International Health Conference convened in New York in June of the same year and the representatives of sixty-one nations in attendance drafted and approved a Constitution for the World Health Organization To carry on until this Constitution could be ratified by at least twenty-six Member States of the United Nations, an Interim Commission of eighteen countries was established This temporary body was dissolved in September 1948 when the World Health Organization came into being The first World Health Assembly was held in Geneva in July 1948

W H O is a specialized agency of the U N devised to function as an inter-governmental health organization It has taken over the work of and has assimilated the Office International d'Hygiène Publique, the Health Organization of the League of Nations, and the Health Division of U N R R A Its functions in the Americas are carried out by the Pan-American Sanitary Bureau, which has been nominated to

Fig 18 A WHO Malaria Control Project in Taiwan A member of the Malaria Control Demonstration Team is spraying a farmhouse kitchen with residual DDT

Courtesy of the Malaria Section WHO Geneva

alleviating great suffering, it fought typhus, typhoid fever, diphtheria, and malaria in Europe, cholera and plague in China, tuberculosis and malnutrition in many countries

The U N R R A Health Division took the initiative and contributed fundamentally in malaria-eradication programmes in Greece and Sardinia, co operating in each case with the local government and, in the case of Sardinia, also with The Rockefeller Foundation These activities illustrate that the U N R R A Health Division implemented some projects that will long have a beneficial influence on public health According to the Rt Hon Philip Noel-Baker, U N R R A constituted 'the greatest act of charity the world has ever seen'

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act as a Regional Office of the W.H.O. Other regional offices have been set up for European, African, Eastern Mediterranean, South-East Asian, and Western Pacific countries.

The work of W.H.O. is carried on by three bodies: the World Health Assembly, which is the supreme authority to which all Member States send delegates; the Executive Board of eighteen persons designated by as many Member States and constituting the executive organ of W.H.O.; and a Secretariat under a Director-General. Within this Secretariat there is a Malaria Section, under Dr. E. J. Pampana, an experienced malariologist and capable administrator. In co-operation with the Regional Offices, the Malaria Section puts into effect the malaria programmes authorized by the Assembly. Some of the Regional Offices have or have had Malaria Advisers in their secretariats.

The Interim Commission in 1947 set up an Expert Committee on Malaria which met that year in Geneva and in 1948 in Washington. The W.H.O. continued the malaria committee which had its third session in Geneva in 1949, fourth in Kampala, Uganda, in 1950, and fifth in Istanbul in 1953. This committee is purely advisory in its functions and it has consisted of an average of nine men whose combined international experience has covered all aspects of malariology, not forgetting that of practical malaria control.

There is a W.H.O. Expert Advisory Panel on Malaria, consisting of malariologists nominated from every part of the world. From this group there is chosen a new set of members of the Malaria Committee each time the Director-General deems it advisable for the committee to meet. There is also an Expert Committee on Insecticides similar to and closely co-operating with the Malaria Committee. The Insecticides Committee has held meetings in Cagliari, Sardinia, 1949, in Geneva, 1950, in Savannah, Georgia, July–August 1951, in Geneva, November–December 1951, and in Caracas, Venezuela, 1954.

The Malaria and Insecticides Committees have prepared reports which have been widely circulated by W.H.O. on vote of the Assembly. These reports have discussed not only W.H.O. malaria policy and programmes, but also topics of

general importance in world-wide malaria control efforts Because these reports are passed upon by the Executive Board and the Assembly after study by governmental delegations they gain additional authority when disseminated

W H O has a number of important accomplishments in malariology to its credit For example, there has been an evaluation of malaria drugs and a standardization of techniques for their trial in hospital and field A W H O monograph on malaria terminology has given precision to definitions and methodology of epidemiologic investigations There has also been welcome standardizing of insecticide formulations, spraying equipment, and methods of testing the effectiveness of toxicants and apparatus—an achievement of great practical importance to governments in the planning and accomplishment of malaria-control projects Hand in hand with these efforts to standardize, there has been a determined effort by W H O to increase the manufacture and to improve the distribution of insecticides and spraying equipment With E C O S O C co-operation, regional production of insecticides has been stimulated and, with U N I C E F help, DDT manufacturing plants are being built in Egypt India, and Pakistan

A great deal of effort has gone into the training of essential personnel for malaria-control programmes There have been fellowships, grants-in-aid short-term lectureships in Mexico, Venezuela, India, Portugal, and Nigeria, International W H O Courses in French in Italy in 1949 and in Portugal, 1951 and 1952, a course in English in Nigeria in 1952 Assistance has been given in the training of local personnel in certain countries and in setting up central malaria institutes in Afghanistan, Iran, Iraq, and elsewhere Expert malaria advisers have been sent to several countries

More recently, W H O has given leadership in regard to the immense problems of malaria control in Africa In 1950 W H O co-operated with the Committee for Technical Co operation in Africa South of the Sahara (C T C A) in convening a Malaria Conference in Kampala, Uganda Experts from all parts of equatorial and South Africa were present, also members of the W H O Expert Committee

on Malaria. As a result of this Conference there is now wide agreement in what may fairly be called an African malaria-control policy.

In 1953 W.H.O. convened in Bangkok the first Asian Malaria Conference, referred to in a previous section. This was attended by malariologists from fifteen countries; representatives of U.N.I.C.E.F. and F.A.O.; also W.H.O. malaria personnel working in Asia or representing Headquarters. The agenda included a review of the status of malaria control, questions of organization and planning of national projects, and the important point of inter-country co-operation and co-ordination in malaria control.

Many data and reports pertinent to malaria investigations and control have been mimeographed and circulated. W.H.O. has also given attention to the need for spraying, quarantine measures, and sanitation at sea and air ports to prevent the introduction or the export of mosquitoes.

Finally and most important, W.H.O. has sent out to various countries, on request, Malaria Control Demonstration Teams. These have usually consisted of a malariologist who is the team leader, an entomologist, a sanitary engineer or sanitarian, and sometimes a public health nurse. The function of these teams is to make epidemiological studies and to demonstrate malaria control by residual spraying under local conditions. The projects represent national undertakings, with W.H.O. technical guidance and key personnel. They are designed 'to give adequate advice and practical assistance to Governments in order to foster the development of local and national malaria control programmes'. The demonstrations are so planned that the continuing cost of control will not be beyond local financial resources. Moreover, the teams are fitted carefully into existing public health structures and are sent only when governments themselves pledge to carry forward the control programmes, if the latter are shown to be advantageous. As a direct result of the work of these teams, several governments that up to 1947 had not done or had scarcely begun to do rural malaria control are now planning or carrying out country-wide schemes to eliminate malaria as a public

health problem an achievement that probably could only have come about through the stimulus of an international agency such as W H O

Control Demonstration Teams have operated during various periods since 1949 in Afghanistan, Borneo, Burma, Indonesia, Thailand, Cambodia, Vietnam, Taiwan, Lebanon, Iraq, Iran, Saudi Arabia, Pakistan, the Philippines, Syria, and India In the Americas, W H O field personnel have assisted in malaria-insect control projects in Bolivia, the Dominican Republic, Haiti and Paraguay The average annual cost for personnel, materials, and equipment has been the remarkably low sum of approximately 15 (U S) cents *per capita* of population protected In several cases, W H O teams have had such convincing results that governments themselves are now carrying on with local funds and personnel Some idea of this important fact may be had from the following figures relating to residual spraying for malaria control (other examples could be cited)

Afghanistan

1951 W H O team protected	147 981 persons
1952 Government itself protected	675 000

Government now plans to do residual spraying in all malarious areas protecting 2 million persons by 1955

Thailand

1951 W H O team protected (second year)	171 957 persons	
1952 Government with Point IV aid protected	1,400,000	,,
1953 Planned coverage	5 000,000	,,

All in all, W H O malaria-control demonstration teams may claim to have stimulated programmes of residual spraying that are now protecting nearly 50 million people

Practical results in many places to date justify trials of residual spraying even before the vectors or their habits are well known But in a few areas there has been doubt about the probable usefulness of residual spraying W H O , therefore, has set up some pilot or experimental control projects, for example, in the Philippines and Sarawak, where vector

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habits of not resting on treated surfaces had been thought to make the use of residual spraying questionable Other experimental projects have been set up by W H O in French Cameroons, Liberia, and Nigeria, where the question is one of what formulation of insecticide to use—DDT, benzene hexachloride, or dieldrin

Many of the Malaria Control Teams have been partly supported by U N I C E F, which has provided materials and equipment Some teams have had similar help from E C A or T C A There has also been co-operation with the Food and Agriculture Organization in some areas where an increase in food production is specially important

In some cases the W H O Malaria Control Demonstration Teams have been able to attack kala azar, filariasis, plague, and other insect-borne diseases In Ceylon, W H O has assisted in setting up a training centre for personnel who will have the responsibility of controlling insect-borne diseases in general

The composition of some of the W H O Malaria Control Demonstration Teams illustrates dramatically the international character of the malaria work For example, in Iran there was a team consisting of an Italian malariologist, a Belgian entomologist, and an American sanitarian, in Lebanon there were Italian malariologist, United Kingdom entomologist, and Egyptian sanitarian, in Taiwan, a Greek malariologist, American entomologist, and Filipino sanitarian, in Thailand, Indian malariologist and entomologist, South African sanitarian, and Irish nurse

In conclusion, it seems fair to say that the W H O malaria activities have contributed significantly to the tremendous advance in the control of this disease witnessed during the past six years More and more nations are thinking and acting in terms of the eradication of malaria as a public health problem within their borders In Asia it seems likely that more than 200 million persons may be under protection from malaria within the next decade Even continent-wide success seems assured in the Americas within a reasonable time The Malaria Section of W H O is, indeed, a key factor in maintaining the remarkable acceleration in

the decline of malaria throughout the world This alone, apart from its many other important health activities, would justify the existence of the World Health Organization of the United Nations

United Nations Children's Fund

The United Nations Children's Fund, universally known as U N I C E F, is not a Specialized Agency but is an integral organ of the United Nations It was created by the U N Assembly in December 1946 on recommendation of the Economic and Social Council The latter body had been led to make this move by a resolution submitted by the late Mayor La Guardia of New York, then Director-General of U N R R A, in September of the same year The donor countries had decided in August to terminate U N R R A at the end of the year but saw grave emergency health problems remaining, particularly in regard to children So they had resolved to donate their residual assets to a children's fund, if such were established by the U N in res

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(*a*) For the benefit of children and adolescents of countries which were victims of aggression and in order to assist in their rehabilitation (*b*) For the benefit of children and adolescents of countries at present receiving assistance from the United Nations Relief and Rehabilitation Administration (*c*) For child health purposes generally, giving high priority to the children of countries victims of aggression

The Fund is administered by an Executive Director appointed by the Secretary-General of the U N, under policies established by an Executive Board in accordance with principles laid down by E C O S O C It is financed by voluntary contributions from governments and private sources In May 1947 the United States made a donation of $15 million to the Fund and authorized a further appropriation up to $100 million on a 'matching' basis whereby

C.T.C.A.

Another recent multilateral organization that has an interest in malaria control is the Commission for Technical Co-operation in Africa south of the Sahara (C.T.C.A.), which was founded in January 1950 in Paris by representatives of Belgium, France, Portugal, Southern Rhodesia, Union of South Africa, and the United Kingdom. The purpose of this Commission is to review periodically those technical subjects on which co-ordinated action can be usefully undertaken by member governments and to prepare joint requests to the Specialized Agencies for assistance. This C.T.C.A. co-operated with W.H.O. in 1950 in sponsoring the African Malaria Conference held in Kampala, Uganda, already mentioned.

16

BILATERAL GOVERNMENTAL AGENCIES

SEVERAL agencies of the United States Government have been concerned to a greater or lesser extent with malaria investigations and control overseas on a bilateral basis For example, one may list the U S Public Health Service, The I I A A or Institute of Inter-American Affairs, the E C A or Economic Co-operation Administration (Marshall Plan) later the M S A or Mutual Security Agency and now incorporated in the Foreign Operations Administration (F O A), T C A or Technical Co-operation Administration (Point Four Programme) now also in F O A , and others

The public health activities of these agencies, which involve direct relationships between two governments, do not reflect any lack of interest by the United States in the World Health Organization These bilateral efforts are co-ordinated with and frequently guided by W H O They are not yet a part of W H O because of the practical consideration that, as a matter of logical principle, no one nation should participate in W H O financing to a greater extent than a third of its total budget, and at present it seems not to be feasible to create large W H O budgets The United States has been willing to spend much more than such an amount in the field of international health and so it has pushed out beyond the present reach of W H O and has continued some and devised other bilateral agencies to make this possible Bilateral programmes involving United States co-operation are now active in no fewer than a third of all the countries of the world

United States Public Health Service

The U S Public Health Service, in addition to essential aid to I I A A , E C A , T C A , M S A , and F O A in advice and in selection of personnel, including assignment of its own officers when required, has assisted in numerous overseas malaria projects although, of course, it is primarily

concerned with the improvement of health in its own land Here it has a notable history of malaria activities which may be briefly summarized in passing

The modern period of interest in malaria in the United States began in 1912–13 when Drs Henry R Carter and R H von Ezdorf started to plan experiments for the control of this disease in the south, and von Ezdorf began the first systematic collection of malaria statistics in America The first malaria headquarters of the P H S were set up at the Marine Hospital in Mobile in 1912 In 1914 the P H S obtained the first Congressional appropriation for malaria investigations

The early malaria-control experiments sponsored by the P H S, and the extensive *Malaria Control Demonstrations*, mentioned later as projects in which The Rockefeller Foundation had the privilege of co-operating, marked the beginning of a remarkably successful attack on malaria by anti-mosquito measures in the southern United States The outstanding malaria-control activities of the P H S in extra-cantonment areas of the south in the First and Second World Wars have already been mentioned The P H S also carried out many early and basic investigations of mosquito taxonomy and behaviour, parasite morphology and staining, impounded waters and railways in relation to malaria, insecticides and insecticiding apparatus A detailed historical study to do justice to the activities of the P H S in malariology should be written

Special mention may be made here of the malaria investigations of Dr H R Carter, L D Fricks, L L Williams, Jr, and V H Haas, at successive field and laboratory stations in Memphis, Richmond, and Washington, of S W Simmons and colleagues at laboratories of the Communicable Diseases Centre in Savannah, and of G R Coatney, Martin Young, and others at Columbia, Washington, and elsewhere It will also be recalled that Marshall A Barber, Theodore B Hayne, and William H W Komp developed the use of Paris green as a larvicide and J A Le Prince and H A Johnson worked out the use of mechanical equipment to spread the insecticidal dust Barber's name is also

associated with many other important malaria investigations carried out while associated with the U S P H S, and afterwards

In 1937 L L Williams, Jr, successfully persuaded State Health Departments to organize Malaria Control Units comprised of physician-entomologist-engineer teams At the same time he proposed that a final attack be pressed home to eradicate the remaining foci of malaria in the United States What an immense source of satisfaction it must be to Dr Williams, now retired, to see how malaria has practically ceased to be endemic within the continental limits of his country No one has done more to bring about this happy state of affairs than has Williams

Malaria chemotherapy investigations by the P H S have been notable and have already been discussed in an earlier section In these studies the names of Dr L F Small, G Robert Coatney, and W Clark Cooper are particularly well known The fundamental experiments with human volunteers during and after the Second World War have already been described in Section II

But the vision of the P H S has extended beyond local boundaries For reasons not alone altruistic, it has been concerned with overseas malaria problems Obviously, it is important to reduce the incidence of those illnesses that, like malaria, lower the effectiveness of millions of farmers in potentially great food-producing regions of the world Such diseases as the tropical fevers, which handicap labourers, also increase the cost of rubber, coffee, minerals, certain fruits, assorted fibres, hardwoods, oils, and waxes Industrial nations are also affected because sickly peoples cannot afford extensive purchases of manufactured products These aspects are probably more basic than they appear to be at first thought Added to them is the fact that malaria is a factor that, among others, helps to predispose a community to infection with political germs that can delay and destroy freedom

The international malaria activities of the P H S date back to the early years of the present century For example, in 1904 the P H S at the request of the Army Medical

Department assigned Dr. H. R. Carter, and others, to Panama for duties under Colonel Gorgas. Earlier the P.H.S. had had an active part in planning and creating the Pan-American Sanitary Bureau and it subsequently provided much of the direction for many years. As related in another chapter, the P.A.S.B. has been much concerned about malaria, among other diseases, of the Americas. Many staff members of the Service have been assigned to this Bureau and the first three directors had been Surgeons General of the Health Service. Several of the assigned staff were primarily active in malaria control.

In 1945 the P.H.S. established an Office, later a Division, of International Health Relations, first under the direction of Dr. J. A. Doull, who was succeeded by Dr. L. L. Williams, Jr. from 1948–53, and now by Dr. van Zile Hyde. This division organized and staffed with Service officers the public health branch of the American Mission to Greece which was continued by the Economic Co-operation Administration and which had much to do with the Greek malaria eradication project already described. The same is true of similar missions to Liberia, to Turkey, to Iran, to Indo-China, and elsewhere. In all of these, malaria-control activities were an important part of the objective.

Mention should be made of the extensive and successful programme of malaria investigation and control carried out by P.H.S. officers in Puerto Rico during the Second World War. Several other P.H.S. officers were notably engaged in overseas malaria-control activities during the war. Finally, there was a post-war Public Health Rehabilitation Program in the Philippines with P.H.S. supervision and this included extensive malaria-control assistance.

Unquestionably, the U.S.P.H.S. has been a powerful force in the modern efforts that have so successfully brought about an accelerating decline in world-wide incidence of malaria.

The Institute of Inter-American Affairs

Shortly after Japan attacked the United States at Pearl Harbour the Foreign Ministers of the American Republics

called for solidarity and they specifically suggested co-operation in health and sanitation programmes Therefore, in 1942, the U S Office of the Co-ordinator of Inter-American Affairs launched a co-operative health programme in eighteen Latin American nations Under the capable direction of Major-General George C Dunham of the Army Medical Corps, a Health Section was set up in the newly formed Institute for Inter-American Affairs (later the Regional Office in Latin America of the Technical Co-operation Administration, a State Department agency that carried out its health activities through a Division of Health, Welfare, and Housing (now a part of the Foreign Operations Administration) The initial five-year plan has been extended and the Health Section is still active Emphasis has been on the development of local health services, sanitation of the environment, and training of professional public health workers Special efforts have been made to control insect-borne diseases, with much emphasis on malaria

Co-operation has been a central key-word in thought and action For example, the I I A A shares responsibility with P A S B and U N I C E F in the integrated insect-control project in Central America already mentioned An important part of the operating mechanism of I I A A has been the so-called *Servicio Cooperativo* This is an administrative unit established as an integral part of the Ministry of Health of a country in which the I I A A is co-operating By agreement, the Chief of the I I A A Field Party in a country serves as Director of the *Servicio*, answerable both to the I I A A and to the Minister of Health The staff of the unit consists of both local and I I A A members At first, of course, the financial contributions of the United States were larger than those of the co-operating countries But now the reverse is true

Malaria was recognized as a serious burden operating against the economic welfare of Latin America, and many believed that it was the major disease problem of the region A majority of Latin American governments had already established national malaria services before the advent of the *Servicios*, so that it was not uncommon, in 1942, to find

that the local authorities had studied the epidemiology of malaria, knew what was required to solve the problems but lacked the means to implement their plans.

During the eight months of 1942, following establishment of the first *Servicio*, there were initiated thirty projects devoted to malaria control. It was realized that the control of malaria more than of any other disease would be a determining factor in the drive to increase the output of strategic materials. Thirty-five new projects were begun in [illegible] in 1944, 32 in 1945, and 12 in 1[illegible] four years, 1947–50, there were [illegible] a total of 163 malaria projects were initiated in a 10-year period, 82·2 per cent. having been started during the war period.

Eleven malaria projects are still active—four based on drainage and seven on DDT.

The 163 projects involved an expenditure, as at June 1951, of $9,522,224. Of this amount, 51·7 per cent. was expended for drainage projects of a permanent character; 39·4 per cent. on drainage of a temporary nature and on larviciding; 5·4 per cent. on DDT house spraying against adult anophelines; 1·5 per cent. on studies and surveys. Thus, more than half of the money expended, a total of $4,926,181, was employed for drainage projects of a permanent character and therefore of lasting benefit to the countries concerned.

The Institute has co-operated with the National Health Departments of fifteen Latin American countries in which work has been done; also with the Pan-American Sanitary Bureau–World Health Organization, The Rockefeller Foundation, and the United Nations Children's Fund.

Many methods have been utilized in carrying out the malaria-control work in Latin America. The earlier programmes were based primarily on anti-larval measures, involving permanent engineering such as draining, filling, clearing bush, and using tide gates. In every case, preliminary entomological and medical surveys of the areas were made. Widespread prophylactic use of anti-malarial drugs was also a part of the programme. When DDT became available it proved very useful, even in such difficult

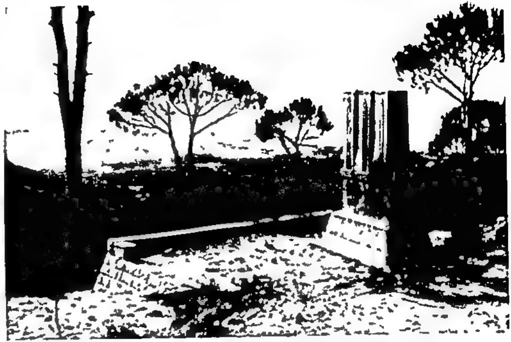

Fig 19 Memorial to Drs Darling and Lothian and Mlle Besson at the place where they were killed in an automobile accident in the hills above Beirut in 1925 while on a Malaria Commission tour in the Near East

Photograph by author

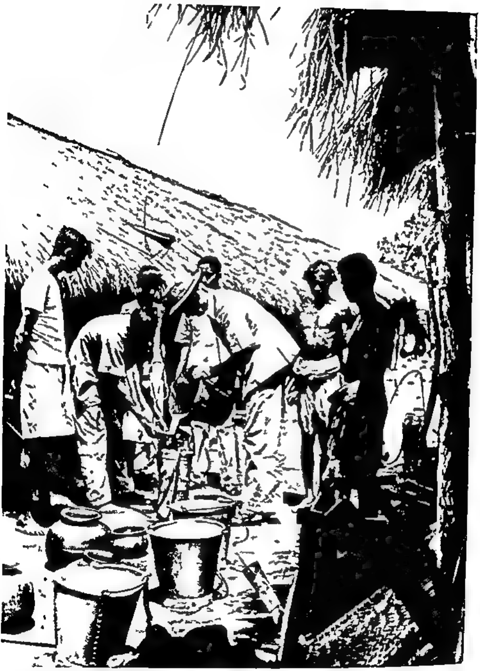

Fig 20 A WHO/UNICEF Malaria Control Project in the Jeypore Hills of India The Malaria Control Demonstration Team leader is giving instruction in the mixing of a DDT formulation for residual spraying

Courtesy of the Malaria Section WHO Geneva

areas as the Amazon Valley Professional personnel such as doctors, sanitary engineers, public health nurses, sanitary inspectors, laboratory technicians, and others were trained in the treatment and control of malaria This was done by special local courses, and by travel grants and fellowships to the United States The malaria-control programme also included education of the general public in malaria prevention and mosquito control throughout the work

Malaria Control Programme
of
The Institute of Inter-American Affairs

Country	*Total cost of all malaria control projects*[2]	*Total cost of all health and sanitation division projects*[2]	*Per cent spent for malaria control*
	$	$	
Bolivia	67,893	4 772 113	1
Brazil	2 529 139	31 357 520	8
Chile	No malaria control programme		
Colombia	3 483 737	9 484 202	37
Costa Rica[1]	14 545	993 365	1
Dominican Republic[1]	268 972	575 000	47
Ecuador	456 102	7 074 431	6
El Salvador	88 058	3 115 505	3
Guatemala	139 904	6 196 736	2
Haiti	477 088	2 475 512	19
Honduras	150 466	2 989 711	5
Mexico	280 023	8 591 082	3
Nicaragua[1]	133 565	970 664	14
Panama[1]	532 056	636 861	84
Paraguay	No malaria control programme		
Peru	126 242	5 879 323	2
Uruguay	No malaria control programme		
Venezuela	774 434	7 288 679	11
Total	$9 522 224	$92 400 704	10

[1] Costa Rica programme closed 14 June 1947 and was reopened 14 Feb 1951, Dominican Republic programme closed 31 Dec 1947 Nicaragua programme closed 5 May 1947 and reopened 31 Jan 1951 Panama programme closed Sept 1945 and reopened 26 Feb 1951 The other programmes have operated continuously Figures relate to first programme as reactivated programmes have not included malaria control programmes Panama started a malaria-control project in Feb 1953

[2] Includes United States Host Government and Third Party Contributions All figures are as at June 1951

In all areas where malaria control was undertaken, the incidence of the disease has been reduced considerably and fertile land areas have been reclaimed for cultivation In an industrial and agricultural area of Venezuela, for instance, the incidence of malaria dropped from 22 per cent to less than 1 per cent after the control programme was inaugurated Pasture lands were cleared of water and an agricultural college now stands on what was formerly a flooded area

Malaria Control Programme
of
The Institute of Inter-American Affairs
1942–53

Country	*IIAA programme started*	*Malaria control programme started*	*Malaria programme transferred*[1]
Bolivia	13 Oct 1942	Nov 1942	Dec 1947 (*a*)
Brazil	17 July 1942	Sept 1942	Jan 1950 (*b*)
Chile	12 May 1943	No malaria control programme	
Colombia	23 Oct 1943	Feb 1944	Still active
Costa Rica[2]	27 June 1942	Dec 1945	April 1947 (*c*)
Dominican Republic[2]	26 Aug 1943	March 1944	Dec 1947 (*c*)
Ecuador	24 Feb 1942	May 1942	Still active
El Salvador	8 July 1942	July 1943	Dec 1947 (*d*)
Guatemala	11 Aug 1942	Sept 1942	July 1945 (*c*)
Haiti	27 May 1942	June 1942	June 1951 (*b*)
Honduras	8 July 1942	Sept 1942	Still active
Mexico	2 July 1943	Oct 1944	Still active
Nicaragua[2]	1 July 1942	Nov 1942	May 1947 (*c*)
Panama[2]	31 Dec 1942	Feb 1943	Sept 1945 (*c*)
Paraguay	29 May 1942	No malaria control programme	
Peru	14 July 1942	Oct 1942	May 1945 (*b*)
Uruguay	18 Nov 1943	No malaria control programme	
Venezuela	18 Feb 1943	April 1943	Nov 1947 (*d*)

[1] Date used refers to the last malaria control project transferred
Agency to which malaria control programme was transferred
(*a*) Rockefeller Foundation
(*b*) National Malaria Service
(*c*) National Health Department
(*d*) Division of Malariology, National Health Department
[2] Costa Rica programme closed 14 June 1947 and was reopened 14 Feb 1951, Dominican Republic programme closed 31 Dec 1947 Nicaragua programme closed 5 May 1947 and reopened 31 Jan 1951 Panama programme closed Sept 1945 and reopened 26 Feb 1951

Another example is San Miguel, El Salvador With completion of a permanent drainage scheme, the malaria parasite rate has fallen to approximately 25 per cent of that found prior to control work From the standpoint of malaria transmission it can be said that San Miguel became the first city in Central America to build out malaria The total expenditure is estimated to be less than 60 per cent of the former annual cost to the inhabitants for medical service and drugs to treat clinical malaria The completed work serves an estimated population of 20,000, making the cost *per capita* $1 34

Marshall Plan—Point Four

A surprisingly large programme of malaria control has developed in various countries with the support of the Economic Co operation Administration (E C A) under the so called 'Marshall Plan', and the Technical Co operation Administration (T C A), set up to implement so called 'Point Four' objectives which had their origin in President Truman s inaugural address in January 1949 Now both administrations have been incorporated into the Foreign Operations Administration (F O A)

Immediately after the announcement in 1947 of the Truman Doctrine for containment of Communism, the American Mission for Aid to Greece was launched This contained a group of U S P H S officers In 1948 E C A took over the project and a public health division was formed within the Mission The malaria-control activities initiated by U N R R A were carried forward most successfully, as already described

Somewhat similar malaria programmes under E C A have been or are being carried out in Turkey, Burma, Thailand, Vietnam, Cambodia, Laos, Indonesia, Taiwan, and the Philippines Many of these projects have been continued after the closing of E C A in 1952 for example, by the Mutual Security Agency (successor to E C A) in Greece and by T C A in other areas F O A has taken under its direction the work of I I A A in the Americas and of the U S P H S in Liberia F O A has planned or is actually

conducting health-control programmes, with much emphasis in most cases on malaria, in Afghanistan, Ceylon, Egypt, Eritrea, Ethiopia, India, Iran, Iraq, Israel, Jordan, Lebanon, Libya, Nepal, Pakistan, Saudi Arabia, Sierra Leone, Syria, Yemen, and elsewhere In all of these health programmes the U S P H S has had a large part in providing staff and technical aid Close co operation with W H O and local health departments has been the rule Both M S A and T C A were under the general supervision of the Director of Mutual Security now Director of the Foreign Operations Administration, in the Executive Office of the President

The objective of F O A in preventive medicine has been to build strong and self-supporting national and local health services This requires widespread public demand in the areas concerned, in order to develop sufficient political pres sure Hence the need for successful demonstrations of effective health services, the training of indigenous technicians at professional and subprofessional levels, and the development of health leadership within a country The key words are 'demonstration' and 'training'

The 'Point Four Programme', with total budgets exceeding $300 million, stimulated the United Nations to set up in 1949 its own Expanded Programme for Technical Assistance—now its foremost service project, carried out as a joint effort of the U N and its Specialized Agencies to build up the strength of member countries along economic and social welfare lines Malaria control has a part in this Expanded Programme which is co-ordinated with the U S Point Four scheme

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MALARIA ACTIVITIES OF THE ROCKEFELLER FOUNDATION

THE Rockefeller Foundation received its charter from the New York State Legislature in 1913, twelve years after the establishment in New York of the entirely separate Rockefeller Institute for Medical Research The latter frequently is confused with the Foundation, which, although it maintains laboratories of the Division of Medicine and Public Health at the Institute, is nevertheless distinct in activities, endowment, trustees, and officers

The charter of The Rockefeller Foundation expresses its purpose concisely in the following clause "To promote the well being of mankind throughout the world" As now organized, the Foundation consists of four divisions—Medicine and Public Health, Natural Sciences and Agriculture, Social Sciences, and Humanities Medical and health interests of the Foundation derive largely from the Rockefeller Sanitary Commission, created in 1909 for the treatment and prevention of hookworm infection and disease in the southern United States So successful was this project that when the Trustees of the newly formed Foundation were considering how to implement the latter's purpose, public health seemed to them of special importance At their first meeting, they decided that 'the extension of hookworm work to other parts of the world would be one of the most productive lines of activity to be undertaken' So a trail-blazing International Health Commission was set up, absorbing and replacing the original Sanitary Commission and designed to cross national boundaries This became the International Health Board in 1917, the International Health Division in 1927, and, combining with a Medical Sciences Division in 1951, it became the present Division of Medicine and Public Health

From the outset, the plan was for the Foundation to 'confine itself to projects of an important character, too large to be undertaken, or otherwise unlikely to be undertaken, by other agencies' Another principle recognized by the Trustees was that, 'no gift of money however large, and no outside agency however wise or good, can render a service of permanent value except insofar as the gift or the agency offers the means or the occasion for evoking from the community its own recognition of the need to be met, its own will to meet that need, and its own resources, both material and spiritual, wherewith to meet it' This point has a corollary which had been included by the Director of the Sanitary Commission in his 'Principles of Administration' in 1909, as follows 'The Commission will seek to hide itself behind its work and to keep to the front the local agencies through which the work is being done'

Mr Rockefeller himself had said, 'The best philanthropy involves a search for cause, an attempt to cure evils at their source', and this has consistently been a guiding principle in malaria projects, as in other activities of the Foundation Mr Rockefeller's wisdom in philanthropy was gained by long practice It is sometimes forgotten that from 1855, when at the age of sixteen he carefully gave away 6 per cent of his first wages, Mr Rockefeller never ceased to make substantial gifts every year of his life—for instance, over $1,000 in 1865, at the age of twenty-six

Wickliffe Rose, a layman, was director of the International Health Commission and the succeeding Health Board from 1913 to 1923 He may properly be called a statesman of public health for he had international vision and great administrative ability He quickly realized that the most important aspect of the attack on hookworm disease was that it afforded an excellent approach to the general practice of public health He was soon aware that hookworm anaemia in the southern United States, in Malaya, and elsewhere was often not separable from anaemia due to malaria This led to a realization that malaria was probably the greatest cause of illness and distress throughout much of the world In his 1915 report Rose said 'Malaria is to be

regarded as presenting the most serious medical and sanitary problem with which we have to contend'

Looking more closely at malaria and discussing the situation with experts of the U S Public Health Service, Rose learned that although the basic facts about mosquito transmission had been established in 1898, yet practically no projects to control malaria by anti mosquito measures were to be found in the southern states Rose, with characteristic perspicacity, saw that the prime reason for delayed application of anti mosquito measures to malaria control was a popular and official doubt as to the economic feasibility of such measures Quoting from the 1915 Annual Report of the Foundation,

> In the case of malaria while methods of treatment and control can be effectively applied under ideal conditions it is still necessary to discover whether the various known measures such as quinine treatment screening and drainage operations can be effectively employed separately or in combination at a cost which will not be prohibitive in those communities which suffer most from the disease

Rose recognized that 'Theoretically, the control of malaria is relatively simple, but as a practical undertaking it has been found extremely difficult'

So in 1915, as the first malaria projects of the Foundation, four co operative experiments were supported One was in an area of 25 square miles and 25,000 persons in Bolivar County, Mississippi, under the administration of the State Department of Health, to test the practicability of malaria control by detecting the human carriers and freeing them of parasites by treatment The other three experiments were organized at the invitation of and in co operation with the U S Public Health Service and local authorities in Arkansas One experiment was at Crossett where control was attempted by curbing mosquitoes with such simple measures as minor ditching cleaning of ditches, and the use of larvicides, and two were at Lake Village, where screening was tested in one group of houses and prophylactic quinine in another

'Gratifying results', with notable reductions of malaria incidence at reasonable costs were reported in 1916 for all four experiments The Crossett community was so well

pleased that in 1917 it assumed both financial and directing responsibilities, at costs of about 63 cents *per capita* per year.

By 1918 there were co-operative projects in four Arkansas towns to test the feasibility of anti-mosquito measures of malaria control Costs ranged from 44 cents to $1 25 *per capita*, malaria incidence declined notably and, as Rose remarked in his 1918 annual report, 'It is not surprising that towns and villages are making appropriations faster than trained sanitarians can be found to undertake the work of malaria control ' Rose reported that

> It is a source of satisfaction that the state authorities in Arkansas have decided to create a special division to deal with malaria control, measures employed to be based upon the demonstrations conducted under the auspices of the International Health Board, and also upon the results which the U S Public Health Service has secured in sanitating, on a large scale, the zones surrounding certain of the army cantonments and camps

Sunflower County in Mississippi, because of the great amount of water surface where *Anopheles* mosquitoes were breeding, was added to Bolivar County for quinine experiments These reduced malaria among some 9,000 persons in 100 square miles at a first-year expense of $1 08 *per capita* Since doctor's bills for malaria treatment in the county had been averaging $5 annually, control seemed like a good investment to the people Rose in 1918 reaffirmed the objective of the malaria experiments which was 'the highest degree of malaria control consistent with a reasonably low per capita cost'

In 1919 Rose was able to state that

> The practical measures for fighting malaria, then, are clearly indicated (1) to eliminate Anopheles by preventing their breeding, (2) to screen the houses against this mosquito, (3) to sterilize by quinine the blood of human malaria carriers In a given demonstration one or all of these methods may be used, according to local conditions

One result of the Mississippi experiments had been the development of a standardized quinine dosage, often called

the 'Bass standard treatment', after Dr C C Bass, who devised it It consisted of 30 grains a day during an acute attack, followed by 10 grains of quinine daily for eight weeks

In June 1919 a conference was held to plan a concerted campaign against malaria in the southern states Representatives of the U S Public Health Service, of State departments of health and of the International Health Board of the Rockefeller Foundation were present A programme was prepared which subsequently was approved and adopted in ten states The object was to test the above-mentioned measures of malaria control on a wide scale and to educate the public in order to arouse support for a comprehensive effort to eliminate malaria from the entire southern United States The Federal and State authorities and the Rockefeller Foundation co-operated in supplying funds and personnel By 1919 the International Health Board listed three regular and nine special staff members assigned full-time to malaria control projects and this figure rose to four regular and sixteen special members in 1920 and 1921 It should be emphasized that in all of its malaria activities in the south, as later overseas, the Foundation recognized that official leadership by the constituted authorities must be maintained The Foundation always remained in the background

The scope of the malaria programme of the Foundation in the south increased rapidly Some fifty-two towns in ten states were aided, in co-operation with Federal and State agencies in 1920 Experiments were extended from urban communities out into rural areas of scattered houses Then, in 1921, malaria-control responsibilities began to be taken over by county health units, to be made a permanent part of the county scheme for co-ordinated health work, directed by the County Health Officer supported by State, County, and local funds and assisted by State personnel such as specially trained malaria-control engineers or sanitarians This gave greater stability to the malaria-control projects

By 1922 the Foundation was aiding malaria control in no fewer than 163 counties in 10 states More than 100 urban

centres had demonstration projects in operation *Per capita* costs of control even in rural areas were averaging about 45 cents In eight State Health Departments by 1922 there were staffs specially trained for malaria control, giving full time to the support of county efforts By 1926, it was possible to report that as a result of ten years' activity along these lines, malaria had practically disappeared from cities and towns of the United States Of course, the rural areas presented a more difficult problem but steady progress was made, largely because of county health unit efforts These were facilitated in 1926 when the Foundation sponsored a standard plan for county malaria-control work Quininization had been found of great value in reducing the severity of illness but not in lowering the incidence of the disease No reasonable doubt at all remained that malaria control required a combination of measures, of which those directed against the vector were most important

The present freedom of the United States from malaria is in no small measure due to those years of active co-operation between the Public Health Service, certain State and County Health Departments, and the International Health Board, linking resources of men and money to find practical ways of controlling malaria Here was an early and powerful impetus towards widespread use of anti-mosquito measures systematically applied to rid the southern states of malaria Before attempting to assess the degree of 'natural recession' of malaria in the United States one should read again the records of the intensive drive against the vector insect, over three decades, beginning in 1916

In 1920, for the first time, the Foundation had extended its malaria programme overseas when it sent a representative to Puerto Rico to make a malaria survey The next year it co-operated in preliminary studies in Nicaragua and Argentina

Dr Frederick F Russell became director of the International Health Board in 1923 and he developed the idea of co-ordinated field and laboratory observations and experiment on a world-wide scale in malaria, as in certain other diseases such as yellow fever. Under his capable guidance

there were many overseas demonstrations of the advantages of fortifying public health administration with concomitant research

Since 1920 the Foundation has assisted in one way or another in field or laboratory studies or in experimental or practical control projects in some fifty-five countries, territories, or colonies, on every continent, investing over $4½ million in this way during the period 1915–50, not including salaries or expenses of staff members As a prototype, the International Health Board in its malaria activities, as in other ways, has expressed a philosophy and has set patterns of procedure for organizations seeking to foster international efforts against preventable disease Moreover, staff members have co operated actively with the Malaria Commission of the League of Nations and in the malaria control activities of the World Health Organization as well as with the Pan-American Sanitary Bureau and other bodies

One of the most successful overseas projects of the Foundation was in Italy, where, from 1924 to 1934, there was co-operation with the Malaria Experiment Station A series of demonstrations proved conclusively that malaria control in Italy, as elsewhere in Europe, could best be achieved by anti-vector measures rather than by mass prophylaxis with quinine or other drugs These brilliant studies by Professor Missiroli, Dr L W Hackett, and their colleagues resulted in widespread acceptance of the usefulness of larvicides in malaria control They were fully corroborated by similar co-operative experiments in Greece, Albania, and elsewhere Here was substantial evidence that malaria control in all Europe would be economically feasible by an attack on the vector insects

In the United States and elsewhere the malaria control studies soon revealed the need for more knowledge of the taxonomy, ecology, and behaviour of malaria carrying mosquitoes in order to make possible a well focused attack at reduced costs The Foundation began in 1921 to co-operate with the U S Bureau of Entomology in such studies and this was the beginning of a programme of entomological studies which continued for more than thirty years, in the

classification, distribution, life-history, morphology, physiology, relationship to malaria transmission, and other aspects of malaria vectors in many parts of the world For example, much of the basic work in the differentiation of the *maculipennis* complex, in the taxonomy of Brazilian and of Philippine *Anopheles* was done with Foundation co-operation

Between 1924 and 1951, inclusive, in the Collected Papers of the International Health Division of The Rockefeller Foundation, there were some 443 articles relating to malariology and 125 to mosquitoes All aspects of malaria, such as avian infections, malaria control, immunity, pathology, transmission, clinical malaria, and so on, were included Staff members have published lectures and textbooks on mosquitoes and malaria, ranging in scope from primers in a dozen languages to textbooks varying in size from pamphlets up to a comprehensive two-volume compendium of 1,600 pages

In 1923 the Leesburg Station for Malaria Field Studies had been established in Georgia There, S T Darling did much to focus attention on *A quadrimaculatus*, the vector in the south-eastern states, and to emphasize species sanitation He also brought spleen palpation into its proper place in malaria surveys in the states where it had previously been largely ignored Much training of personnel was done at Leesburg and also at stations in Brazil, Italy, Corsica, and elsewhere, during the years following 1923

Studies in malaria parasitology, immunity, or treatment were supported from 1925 or later at Leesburg, Georgia, Edenton, North Carolina, and Tallahassee, Florida, under Doctor M F Boyd, at the University of Chicago under W H Taliaferro and C G Huff, at Johns Hopkins under Professor R W Hegner, at the Molteno Institute, University of Cambridge in England, under Dr S P James and colleagues, in Rome under Professor Alberto Missiroli and his associates, at the Foundation Laboratories in New York, under L T Coggeshall and later Dr Max Theiler and their colleagues, and in laboratories in other parts of the world Out of these studies came many fundamental advances in regard to the life-cycle, physiology, and metabolism of the

parasite, its relation to clinical malaria and its response to drugs

The co operative malaria demonstrations and studies in which the Foundation participated resulted directly in the formation of many state and national malaria control and investigative organizations As examples, the following may be mentioned but by no means constitute a complete list Bureau of Malaria Control, Puerto Rico, Malaria Commission, Cuba, Malaria Section, Panama, Division of Malariology, Venezuela, Malaria Laboratories of the Institute of Public Health, Rome, Malaria Division of the School of Hygiene, Athens, Malaria Institute at Aguas de Moura in Portugal, Southern Branch of the Malaria Institute of India

Finally, it may be of interest to describe briefly three somewhat dramatic projects in which the Foundation had a part These were the vector eradication schemes in Brazil, Egypt, and Sardinia

Gambiae Eradication in Brazil

On a Sunday morning in March 1930 Raymond C Shannon, an entomologist on the staff of The Rockefeller Foundation, found *Anopheles gambiae* in Natal, Brazil This was of great interest because *A gambiae* is a notorious malaria carrying African mosquito Possibly a plane but more likely a fast French mail steamer or destroyer had taken a small number of these insects from Dakar to Natal, and the stowaways had succeeded in colonizing in the New World

By 1931 the species had spread 115 miles up the coast, stimulating local conventional anti malaria campaigns These had some success and lulled the health department into a sense of complacency which was completely shattered in 1938 when *A gambiae* caused what was probably the greatest epidemic of malaria ever seen in the Americas During the first six months there were over 100,000 cases with at least 14,000 deaths It became apparent that the African invaders had extended over more than 200 miles, north and west of Natal and that they threatened to invade all of northern

Brazil. Thereafter, they would almost certainly push on into Central America, with devastating results.

Displaying both courage and wisdom, the Brazilian Government decided that the usual anti-malaria measures would not be sufficient to meet the threat. They deliberately planned to eradicate every *gambiae* mosquito in the country. The complete extirpation of a species of mosquito had never been accomplished and a majority of experienced malariologists at that time would doubtless have judged it an utter impossibility. Only one successful scheme for the eradication of a disease-bearing insect was then on record. This was the elimination by Portuguese authorities of the tsetse fly, *Glossina palpalis*, from the small island of Principe, off the Guinea Coast of Africa, thus saving a highly profitable coffee industry.

By presidential decree, in 1939, the Malaria Service of north-east Brazil was created. It was organized as an anti-*gambiae* rather than anti-malaria service. Under the guidance of Drs. Fred L. Soper and D. Bruce Wilson, of the staff of The Rockefeller Foundation, this Brazilian organization, much of which had had years of training in anti-*Aëdes* work, grew to be 4,000 strong and was allotted total budgets of more than $2 million. The entire infested area, and a little beyond, was divided into squares of workable size; an adequate control unit was assigned to each square; and there was simultaneous and meticulous application of Paris green to breeding places and of pyrethrum spray-killing to adult resting places.

The result of this determined and systematic attack was the complete eradication of *A. gambiae* from north-east Brazil and thus from the New World. The invading marauder had been thrown out of a continent, truly a magnificent achievement! The last evidence of *A. gambiae* mosquitoes in the area was obtained on 14 November 1940. In January 1941, all anti-*gambiae* measures were suspended but a large staff of trained men constantly combed the area and contiguous zones for the insect, and there was a standing cash reward for finding it. Not a single living larva or adult of this species could be found in 1941 or 1942. In September

1943 it was reported that two male and three female adult *A gambiae* were taken alive in a Natal hut near a naval anchorage for transatlantic aircraft It seems certain that they were a new lot of stowaways and their discovery led to energetic international efforts to make such transportation of insects by civil or military aircraft impossible No other *gambiae* mosquitoes were found in that year or the two following, and up to the present time Brazil has continued to be free from this troublesome visitor

Here was a great victory, a sanitary triumph! It was the first and, so far, only planned eradication of a mosquito species from a continent Great though the cost of the Brazilian campaign, it was incalculably less than the toll that *A gambiae* would have exacted in the long run had it been curbed by usual anti malaria measures rather than extirpated by a new and bold technique

Eradication of A gambiae from Upper Egypt

The first indication of a *gambiae* invasion of Egypt came in March 1942, when it was learned in Cairo that devastating malaria epidemics were in progress in the Upper Nile Valley, not far from the Sudan border The initial survey showed over 70 per cent malaria positive smears among some 8,800 [illegible]

had ceased

It became evident that the malaria epidemic was due to *A gambiae*, which had extended its range as far as 25 km north of Asyut by November 1942 This northernmost outpost was dealt with and *gambiae* thereafter did not succeed in passing Asyut The invaded area was a narrow strip of cultivated land in the flood-plain of the Nile, some 4,270 square km in size, with a population of some 3 million *Anopheles gambiae* larvae were found in all kinds of breeding places, including mud cracks, rock and sand pools, borrow (*birka*) and brick pits, concrete pits and wells, culverts, irrigation ditches, lakes with matted vegetation The adult

maintained its domestic habits, feeding and resting freely in human habitations

Control began in 1943 and continued until the end of August 1945 The Egyptian Government was assisted by Allied Military Forces, which supplied over 100 vehicles, large quantities of Paris green and pyrethrum and some personnel, including two British units The Rockefeller Foundation co-operated by making available the services of Drs Fred L Soper, D Bruce Wilson, and J Austin Kerr, all of whom had had experience in *gambiae* eradication in north-east Brazil Each took a major part in the Egyptian scheme

The project was soon well organized, with men for dusting, for scouting, and for some house disinsectization At its peak in 1945, the staff totalled 4,182 A group of nearly 1,000 doctors and inspectors carried out a therapeutic service with distribution of free anti-malarials, chiefly atebrin Approximately 138 tons of Paris green were used in a 1 per cent mixture made with any available unsifted dust or sand found at the site of application Nearly 186,000 litres of pyrethrum insecticide were sprayed In 1945, when DDT became available, it was used on a limited scale for residual treatment of railroad wagons, aeroplanes, and boats

The last *A gambiae* was found on 19 February 1945, and the last larviciding was done in August of the same year Some 1,200 scouts were kept on and during 1949 examined about 60,000 houses a week Now, yearly surveys are carried out and, despite some false alarms, it is not believed that any *gambiae* have been in Egypt since February 1945

Species Eradication Attempted in Sardinia

In Sardinia was carried out the famous ERLAAS experiment This project was set up in 1946 by Dr F L Soper of the Foundation and Mr S Keeny of U N R R A to find out whether or not it is feasible to eradicate a malaria-carrying species of mosquito that has been in an area for centuries and thus has made itself thoroughly at home It was known that a recently established mosquito could be

eradicated, for this had been done in the case of African *gambiae* in Brazil, as already described It was also clear that malaria can always be controlled by curbing a guilty mosquito, reducing its numbers to a point at which the species cannot successfully maintain transmission in an area The new question was whether or not malaria control by extirpation of an indigenous malaria-carrying insect would be cheaper in the end than yearly insecticidal programmes that would gradually eliminate the disease but leave some mosquitoes

Leading Italian malariologists co-operated with E C A, U N R R A, and the Rockefeller Foundation in a five-year experiment under the direction successively of D B Wilson, J Austin Kerr, and J A Logan, assisted by F W Knipe, T H G Aitken, John Maier, G V Casini, J A Patterson, and others Costs totalled $12 million, approximately $2 *per capita* per year Thousands of scouts sought out every possible breeding place of the malaria mosquitoes, and all foci were mapped and regularly larvicided with DDT in oil Some were drained or filled Adult mosquitoes were killed by DDT house spraying The result was that Sardinia was freed from malaria But the guilty mosquito, *Anopheles labranchiae*, probably by reason of its centuries of adaptation to all types of breeding places on the island, succeeded in escaping complete annihilation Moreover, *Anopheles sacharovi*, another potential malaria vector, was found in Sardinia after the end of the ERLAAS project Both species now exist there but the numbers are insufficient to propagate malaria Probably a yearly DDT house-spraying programme will check further resurgence and so will continue to prevent malaria But the experiment appears to have confirmed the majority opinion that it is more practical in most places to eliminate malaria by regularly spraying habitations with residual insecticides, as has been done under comparable conditions in Sicily and on the Italian mainland, than by attempting to eradicate the transmitting mosquito, as in Sardinia In each case there must be continuing vigilance and control so that neither method has complete finality

Conclusions

Concluding this section on international aspects of malariology, I believe it will be agreed that the subject has indeed some important international facets that are in refreshing contrast to political bickering and selfish aggression. Certainly, never before in all history have so many nations joined forces so effectively over so great a portion of the earth's surface to attack a specific disease. In a world of dissension and pessimism here is a brilliant ray of hope and promise.

SECTION V

MALARIA AND SOCIETY

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MALARIA PROPHYLAXIS AND POPULATION PRESSURE

In the foregoing sections the story of how man has developed a mastery of malaria has been outlined Undoubtedly, the remarkable decline in the prevalence of this disease has effected and will continue to give rise to important social changes

The impact of the disease malaria on communities has never been uniform throughout the world To some peoples, as in parts of Africa, India, and the Middle East, malaria has been a chronic and sometimes overwhelming handicap that has made economic and social progress difficult or impossible, and at times it has been a direct cause of depopulation and decadence To others, as in the United States, malaria has been but a nagging nuisance, sometimes intolerable, causing steady damage to a considerable number of communities but unable to withstand the tides of progress In still other countries, as in Canada, the disease has had only indirect and almost imperceptible influence

So, too, the effects of malaria control vary greatly In some regions, as in tropical Africa, it has been too limited to have had any measurable influence on the lives of many people and, strange to say, there is some debate as to whether the eradication of paludism could have beneficial effects Some authorities believe that many native Africans have inherited or developed such strong tolerance to malaria that the disease is relatively harmless to them and therefore is not a socially retarding factor These observers fear that,

Conclusions

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by preventing the nightly reinfections that presumably keep tolerance at effective levels, malaria control would be not a boon but a bane, leading directly to malaria epidemics and to serious social disruption Other equally qualified malariologists believe that malaria control, if properly maintained, would be a powerful factor in opening many African communities to agricultural, economic, and social development

Incidentally, some Africans believe that malaria, in areas such as those on the West Coast, has been an ally, striking down and thus greatly limiting the acquisitive powers of the non-immune white 'invader' In the words of S D Onabamiro, a Lecturer in University College, Ibadan, Nigeria, 'Let us give thanks therefore to that little insect, the mosquito, which has saved the land of our fathers for us We cannot sing its praises too often The least we can do is to engrave its picture on our National Flag'

Elsewhere, as in Sardinia, Ceylon, Bombay and Mysore States, the Himalayan Terai in the Uttar Pradesh State of India, Venezuela, Brazil, and other places, current malaria-control projects have removed ancient barriers to progress, making usable many thousands of acres for agricultural development, and also stimulating industry, hydro-electric schemes, fisheries, tourism, and many other kinds of endeavour In a few countries, as in British Guiana and Ceylon, malaria control has so dramatically lowered death-rates that it has aroused pessimistic warnings about 'demographic realities' In Ceylon, for example, the death-rate has recently been halved, mainly by successful anti-malaria measures Noting this sort of phenomenon, Sir Charles Galton Darwin, very bluntly, and in what seems to me a typical 'have-you-stopped-beating-your-wife?—Answer yes or no' query, asks, 'But is the world the better for having a large number of healthy people dying of starvation, rather than letting them die of malaria?'

Moreover, as Professor Hill has pointed out,

> It is *not* a question only of food, if a higher standard of life is to become universal with education communications, housing, reasonable amenities, and public health, a far greater demand will be made on all such natural resources as power, chemicals, minerals, metals,

water, and wood One is left wondering how long these can possibly take the strain

The satisfaction of malariologists has thus been disturbed They are asking themselves some basic questions, as today are physicians and sanitarians generally Has disease prevention become too effective, too widespread? Must DDT, for example, be withheld from densely populated countries?

Traditionally, the science and the art of medical and public health practice are not more basic or more vital to the profession than is a time-honoured obligation to relieve and to prevent illness *without reservations* For reasons of human fallibility, as well as of ethical doctrine, it is highly illogical to deny this obligation for the sake of presumed future good How can we properly refrain from applying those curative and preventive practices that our profession requires of us because we are told that possible future evil may result? Have we the requisite prescience to justify such a serious breach of medical ethics?

Speaking practically, is there in the world today any place where the actual condition of the people has been demonstrably worsened by malaria control? To what extent does the gain in manpower, through reduction of the debilitating effects of malaria, counterbalance the additional need for food? What is the effect of malaria control on community efforts to raise the standards of human welfare? Must we purposefully allow humans to suffer and to die of malaria because of population pressure dangers that stem largely from failure to utilize or to distribute available resources? Is there no solution but higher death-rates?

We all realize, I believe, that rapid growth of population in areas already densely peopled, creates problems that cannot be solved merely by improving public health We also know that the world's population is increasing It approaches 2,500 millions and some demographers assume that if existing trends continue, the total by the year 2000 will exceed 4,000 millions But Notestein, after carefully examining the question, says that the only way to test such an assumption is to keep alive until that date However, at the

present time, often in response to malaria control, death-rates in certain areas are more and more frequently falling below birth-rates, a phenomenon that in time could make it impossible to raise the world's living standards It might even tear them down, in spite of modern technology

This possibility, remote though it may be, excites much comment in which an apprehension about mortality seems to overshadow all other considerations And although many factors are involved in the increase of populations, the effect of controlling disease is so plain that physicians and sanitarians are sometimes held chiefly or even solely responsible for the ills of overpopulation, present and expected More and more frequently we read of 'dangerous doctors', of sanitarians who are 'setting the stage for disaster' We even see the word 'fortunate' applied 'from the demographic angle' to the estimate that only 12 per cent of the world's population is yet receiving any large proportion of modern health service

Increasingly, it is being implied that health officers and sanitarians must slow down or even stop their efforts to control important diseases in overcrowded tropical areas Effective malaria control in British Guiana, for instance, has been deprecated because the immediate result has been an increased birth-rate and a decreased infant mortality Sanitarians consider the successful use of residual DDT in that country an outstanding achievement But certain Jeremiahs react to it by printing such comments as 'The gadgets of short-term public health can speed the production of festering slums much faster than was possible in the past'

Again, progress in control of malaria and other communicable disease in Puerto Rico is viewed by some observers as merely another aspect of a debâcle The new vital tools of public health practice are said to be 'creating problems faster than they are solving them' One writer concluded that in Puerto Rico 'The United States, having provided just enough minor health improvements to ensure more births than deaths has unwittingly encouraged the survival of the unfittest to an extent scarcely equalled in the entire civilized world'

Many similar and equally disconcerting quotations could be given More and more numerous are the sociologists and sanitarians who question the worthwhileness of intensive malaria control in densely peopled countries The calibre of some of the doubters is so outstanding that one must emphasize the importance of their statements Most of them take the view that heightened population pressure is due to the use of asepsis, vaccines, environmental sanitation, insecticides, and antibiotics of the last hundred years The fact that improved agriculture, irrigation, and housing, development of mineral and fuel resources, expanded transport, and growth of strong central governments, as well as other factors, also favour increased populations is seldom mentioned For example, Willcox estimated that the population of Asia was $2\frac{1}{2}$ times greater in 1850 than in 1650, a growth that obviously was not due to vaccines and sanitation Actually, the rate of increase in Asia, by these estimates, has been slower in the era of development of modern preventive medicine, 1850 to 1935, than it was between 1650 and 1850, in the ratios of 1 6 as against 2 5 But the important point is that we are discussing a trend of thought that appears to be gaining adherents and that deserves careful attention Here is no 'straw-man' to tilt against but a serious drift of opinion of which account must be taken

We have no desire to be doomed by unrealistic hopes to attempt the impossible and thereby to fail to achieve more modest improvements in human welfare We know that this task of developing greater health and more ample livelihood from the environment is the oldest and will probably be the longest lasting of all the occupations and preoccupations that concern man But, having studied the progress of the nineteenth century and witnessed that of the first half of the twentieth, we cannot accept pessimism as a logical substitute for progressive community action

The population problem obviously is complicated, exceedingly so, and only one or two of its facets can be mentioned here For example, Verhulst in 1838 and Pearl and Reed in 1920, described a logistic curve that indicates that

populations of animals or man do not expand indefinitely without limit The curve of growth always levels off and becomes asymptotic with a flattened plateau But there is no inevitable rate of population growth The primary forces of natality and mortality are frequently modified by changes in political policy, public health, food-supply, industrial production, the status of women, and many other economic, political, and social factors As to food, for instance, who knows which experts are correct when they variously state that today's knowledge of agriculture could produce adequate and nutritious food for populations of 4,000, 5,000, and even up to 13,000 million people? Who can estimate the effect in the future of greater saving of rainfall and the economic utilization of sea water for irrigation, of vastly multiplied 'fish farming', of widespread practical photosynthesis, of the production of proteins from grasses by high-pressure extraction, of the cultivation and use of unicellular aquatic organisms of fresh and sea water, of the production of food from chemicals, woods, and crops that are not edible today? The equation of population and food is vastly more complicated than any present formulation

Weaver makes this crystal-clear in his superb summary of facts about the three main variables—people, energy, and food

Nevertheless, as Sir Charles Darwin points out, one might visualize a natural population growth of a millionfold during the next 2,000 years, but it is hardly possible to imagine a comparable increase in food-supplies So, from the long-term point of view, calculations as to rate of growth of population and of food-supply are not pertinent except, as Notestein points out, that

> they demonstrate a principle that many people are unwilling to face Sustained population growth, even at a relatively low rate, is not possible for any period of time significant in the history of the human race In principle, there must come a time at which low death rates could not be maintained without comparably low birth rates This is an inexorable fact of nature Death rates must rise or birth rates must fall

On this point there can be no logical argument

Some contemporary commentators on this difficult subject revert to the Malthusian dilemma It will be recalled that, at the end of the eighteenth century, Malthus (1798) concluded without the help of today's knowledge of public health soil science, plant genetics, and many other pertinent variables, that population growth is determined principally by three factors, namely, war, disease and, most of all, food-supply Since he believed that population would always increase faster than food supply, Malthus saw a dilemma he said in effect, either more people must die or else human misery must increase—higher death-rates or greater suffering

The story of Thomas Robert Malthus is an interesting one He was born in 1766 near Guildford, Surrey, the son of Daniel Malthus, who had been a friend and one of the executors of Rousseau Malthus took orders in 1797 and for a short time held the curacy of Albury in Surrey He married in 1805 and soon after was appointed professor of modern history and political economy in the East India Company s college at Haileybury, where he died in 1834

Daniel Malthus, the father was an admirer of Condorcet and Godwin and he agreed with them as regards the perfectibility of society He discussed this subject with his son, who believed that population always tends to outstrip the means of subsistence so that the theories of perfectibility could never be more than wishful thinking Much impressed by his son's original and forceful arguments Daniel persuaded Thomas to put them on paper and having read them he suggested that they be printed as a pamphlet So in 1798 Thomas published the first edition of his *magnum opus, An Essay on the Principle of Population as it affects the future Improvement of Society, with Remarks on the Speculations of M Godwin, M Condorcet, and other Writers* This was so brilliantly written that it aroused great attention and then a storm of controversy Whereupon Thomas set to work to collect data bearing on population increase, going as far back in time and as far afield in the world as he could

Five years later, in 1803, Malthus published an enlarged and emended second edition which was followed from time

to time by still other editions, the sixth and last during his lifetime appearing in 1826 Beginning with the second edition, which substantially modified the original theory, the essay had ceased to be a pamphlet and had grown into a scholarly treatise which was further revised and lengthened in the later editions Malthus also wrote a number of important works on the subject of economic theory

Malthus, in his *Essay* of 1798, started with two postulates 'First, that food is necessary to the existence of man Secondly, that the passion between the sexes is necessary, and will remain nearly in its present state ' Then Malthus on the basis of these beliefs said that

> the power of population is indefinitely greater than the power in the earth to produce subsistence for man Population when unchecked increases in a geometrical ratio Subsistence increases only in an arithmetical ratio A slight acquaintance with numbers will show the immensity of the first power in comparison of the second By that law of our nature which makes food necessary to the life of man the effects of these two unequal powers must be kept equal This implies a strong and constantly operating check on population from the difficulty of subsistence This difficulty must fall somewhere and must necessarily be severely felt by a large portion of mankind

Malthus continued,

> That population cannot increase without the means of subsistence is a proposition so evident that it needs no illustration That population does invariably increase where there are the means of subsistence the history of every people that have ever existed will abundantly prove And that the superior power of population cannot be checked without producing misery or vice the ample portion of these too bitter ingredients in the cup of human life and the continuance of the physical causes that seem to have produced them bear too convincing a testimony

These arguments bring Malthus to the conclusion that

> famine seems to be the last the most dreadful resource of nature The power of population is so superior to the power in the earth to produce subsistence for man that premature death must in some shape or other visit the human race The vices of mankind are active and able ministers of depopulation They are the precursors in the great army of destruction, and often finish the dreadful work them

selves But should they fail in this war of extermination sickly seasons, epidemics, pestilence, and plague, advance in terrific array, and sweep off their thousands and ten thousands Should success be still incomplete, gigantic inevitable famine stalks in the rear, and with one mighty blow, levels the population with the food of the world

Many students, as for example Kenneth Smith in his comprehensive and critical analysis of the Malthusian Controversy, have pointed out that Malthus was not the first to put forward such views Condorcet, for example, has as much right to claim discovery of the principle of population But he avoided pessimism and advocated fewer births Malthus also took from Robert Wallace (1753) the belief that the power of population is so much greater than that of food production that sooner or later the world would be overpopulated and famine would inevitably exert a levelling effect Malthus added his own ratios but these have never been proved As Smith points out so clearly, the arithmetical ratio of Malthus is questionable and the geometrical ratio almost equally unsound Food-supplies have often multiplied much more rapidly than has mankind And there is no proof of a continued geometrical increase of man Malthus cited the instance of vice and misery but he never succeeded in tying them in with his principle very strongly Quoting Smith, 'It is this irrational fear of a full world the legacy of Malthus, which scatters alarm, leads to gloomy forebodings, and hinders a rational approach to the problems of population growth and the standard of living' [illegible] quoting Smith, 'Without belittling Malthus's influence [illegible] the age in which he lived it remains true to say th[illegible] *Essay on Population* is mainly of historic interest, w[illegible] first edition as the most interesting specimen'

Even to this day, however, there continues [illegible] irrational use of Malthus's word 'dilemma' Actu[illegible] not faced with a dilemma at all We face a pro[illegible] this is an entirely different matter Of course [illegible] increasing population pressure with its conc[illegible] eventually the death-rate must rise or the b[illegible] fall But since the latter event, namely, a l[illegible] of the

birth-rate, would be helpful rather than harmful, there can be no true dilemma, no horns of equally undesirable alternatives. We face, not a choice between two evils but, on the contrary, a task well within the scope of man's intelligence and technological potentialities. Evidence already available indicates that this problem can be solved. Slowly but definitely it becomes apparent in the East and in the West that *restraint of birth has equal importance with restraint of death and that one is no more illogical or impossible than the other.* As a matter of plain logic the only humanitarian solution for the population problem is the control of fertility.

What are some of the conditions that already are known to lower birth-rates? According to Thompson, urban birth-rates are usually lower than rural, and the rate decreases as the size of cities increases. Again, the higher the economic status the lower the birth-rate, as a rule, whether rural or urban; the more skilled the father in his trade, the lower the birth-rate, and the more schooling possessed by the mother, the lower the birth-rate. These are general findings which indicate that birth-rates fall, albeit gradually, as standards of living and education rise. In such observations it has been commonly reported that planned parenthood has been the chief cause of lower birth-rates. Such factors as ambition to get ahead, desire for more comfort and greater freedom, efforts to maintain higher family standards of living, hopes that because they are fewer, the children will be better educated and will have greater opportunities to succeed, all these motives become more powerful as community welfare rises to higher levels. All tend to lower the birth-rate.

Better education, more productive agriculture and industry are obvious social needs. But they cannot be expected in a community where disease is unchecked. Also, the absence of public health, with resultant high death-rates, has fostered the growth of social systems that are responsible for high birth-rates. For these reasons, among others, the problem of population densities will not be solved by neglecting to suppress disease at home or abroad, by utilizing deliberately those forces that heedlessly destroy human

lives and cultural institutions Rather, modern health practice should be a major activity around which other public services will combine their efforts to change the social fabric for the common good Experience teaches that without reasonable public health there will not be much planned parenthood or development of public welfare

But we are told by some neo-Malthusians that we should reduce medical and public health practice in crowded tropical areas in order to concentrate our attention on those factors which they believe will tend to create that essential force of public opinion that will bring birth-rates down to equality with death-rates Attempt economic development, improved agriculture, and mass education first, they say, postpone energetic malaria control until there is a widespread desire for family limitation One observer, having questioned the advisability of active public health practice in China, agreed that ' it will seem rank heresy to propose that during the next twenty to thirty years not even severe epidemics in China should be attended with every means available to modern medicine The future welfare of the Chinese people is more dependent on the prevention of births than on the prevention of deaths ' Such authors seem to suggest,

> Don t check diseases like malaria with modern weapons in such places as India or China because you will upset nature s balanced human ecology You will increase population pressure thereby adding to human misery For the present let disease keep down the population Then while pestilence kills off surplus children we will raise the economic level develop education increase the food supply, and implant in the people a desire for limited families Afterwards it will be safe to introduce the newer public health gadgets like DDT

Such a view has even been called 'humanitarian thinking' but to me it seems utterly inconsequential and without foundation in fact or morals a crude policy without a single success on record When the physician and sanitarian forsake that fundamental principle, *the preservation of human life*, they go adrift in dangerous waters How can one properly blame public health practice for 'upsetting a balanced ecology' in disease-ridden countries where for

centuries the average farmer has not had enough to eat! How can one hope that the social progress required to bring about lower birth-rates will be developed in communities having high infant and general death-rates from endemic and epidemic malaria? Who is to be the Solomon who determines where malaria control efforts, for example, should be slackened? Certainly, it would seem that anyone attempting today to decide what populations should be deprived of modern disease control practice, would 'create problems faster than he could solve them'

Obviously, malaria control and other health improvements in some countries have and may outrun social developments They do not have to travel very fast to do so But this leadership, while it emphasizes the need for giving more attention to other aspects of human welfare, cannot logically be designated a cause of an already existing imbalance We must not be deceived by that vivid word, 'balance' There is the sort of equilibrium obtained in a delicatessen store by removing a pickle from the heavier side of a scales, but this is not in any way analogous to obtaining a balanced ecology in human society Withholding public health cannot possibly restore a balance that never existed in the past, and that never can be had in the future without public health Improved agricultural methods, more industrialization, better general education, intelligent control of population growth, these have been obviously desirable for a very long time and must have much greater emphasis But how can they be added in any volume to a society that lacks good health? Widespread family planning becomes possible only when standards of community health and living are raised considerably above minimum subsistence levels Large families are much striven for where economic levels are low, because children are a source of cheap labour, they are thought to be the poor man's wealth and his only hope of support in old age

The needs are apparent Huxley, for example, and many others have emphasized the importance of a positive population policy for the world as a whole and for each nation in it Future generations must not be born into increasing

misery The human race must not be allowed to suffer genetic degeneration We realize this but we do not agree that the answer lies in a curtailment of the practice of community medicine, in a calculated neglect of environmental sanitation and a fostering of malaria On the contrary, the responsibility and task of physicians and sanitarians today seem to me to include an expansion of their efforts to combat preventable diseases The sooner malaria ceases to be a public health problem, the sooner will be added to specialized practice an essential and determined attempt to organize team work with other scientists and educators, particularly in overcrowded areas, in order to devise and operate logical population practice A major and specific effort undoubtedly should be made to bring together geneticist, mathematician, and physiologist, with medical and sanitary scientists, for the advancement of the much neglected study of human heredity and population growth

The fact that those whose type seems most useful in human society today are apt to be first to limit their families is not necessarily an argument against planned parenthood but may in fact be an incentive to extend the practice, surely not an impossibility in the light of the history of social reform and progress, which generally start at the top Is it a certainty that, except in a thin upper stratum of society, man's thought processes and reason will never guide his emotions and instincts?

Too often the phrase 'population policy' connotes simply some contrivance or other for stimulating migration or for encouraging or discouraging childbearing While regulation of family size in most cases and migration in some are indeed basic needs, yet a population policy should permeate the whole fabric of social life There are required practical programmes that will combine the techniques that influence birth and death into a logical and balanced community effort *Man, who has so brilliantly devised measures for restraining death, may be expected to have similar success in regulating birth* And, it is reasonable to believe that the necessary social changes can be made more quickly and more thoroughly where control of disease is most effective

Of course, one cannot expect human beings to accomplish a perfect timing of effort that would completely avoid population pressure But the forces concerned are controllable It is not entirely unreasonable, for example, to imagine that, since lack of balance in international fertility levels is at the centre of the world population problem, there may one day be a 'League of Stationary Populations' with international agreement to control numbers of people, as suggested some years ago by Professor J S Sweeney

In this connexion, Bertrand Russell once said,

> I am inclined to think that the most important of Western values is the habit of a low birthrate If this can be spread throughout the world, the rest of what is good in Western life can also be spread There can be not only prosperity but peace But if the West continues to monopolize the benefits of low birthrates, war, pestilence and famine must continue, and our brief emergence from these ancient evils must be swallowed in a new flood of ignorance, destitution and war

It seems to me that the world needs today not more disease but more vision! The real danger is not malaria control by DDT but domination of intelligence by fear Why emphasize the depopulating powers of death? How infinitely more intelligent is the idea that family size should be such as will permit economic opportunity, health, and social welfare for all! Well-being of child, parent, and community—here is an objective of responsible parenthood that is not unattainable, and towards which remarkable progress has already been made in the Orient as well as in the Occident

Here I should like to quote again from Professor Hill's masterly address on *The Ethical Dilemma of Science* He closed his remarks by saying,

> It is true that scientific research has opened up the possibility of unprecedented good or unlimited harm, for mankind but the use that is made of it depends in the end on the moral judgements of the whole community of men It is totally impossible now to reverse the process of discovery, it will certainly go on To help to guide its use aright is not a scientific dilemma, but the honourable and compelling duty of a good citizen

So we should not be deceived Physicians and public

health officials cannot help mankind by reversing present trends in their practice and by withholding DDT and other modern aid! Rather, it is essential that we maintain our ideals of service We can lead the way with balanced medical and health care programmes, designed for sustained public welfare As stated by the Economic and Social Council of the United Nations in its 1952 report on the world social situation, 'The advance of any community depends on the extent to which it reduces the burden of ill health

Few would deny the need for a closer meeting of the biologic, economic, medical, and social intellectual disciplines that might shed light on the problems of human ecology, and specifically on those of human reproduction Cross fertilization between these fields of learning would no doubt bear splendid fruit Public health as a whole and malariology in particular have had the advantage of well-focused objectives, well-defined specialties, and well-trained personnel They have led the way! Instead of suggesting that sanitarians should curtail their practice, how much better to use public health as that rallying point around which, as suggested by Raymond Fosdick, men of differing cultures, disciplines, and faiths may combine, joining their efforts in the common cause

That physicians, malariologists, and sanitarians integrate their activities with those of agriculturists, demographers, social scientists, economists, educators, political and religious leaders is of the utmost importance For only thus can there be joint planning of social reorientation that will result not in bigger populations but in healthier communities In this way there will be accelerated progress towards higher planes of health and living In the framework of co-ordinated efforts there seems to me no reason why malariologists and other medical and public health practitioners should not continue to play their chosen parts, confident in the conviction that they are contributing to the well-being of mankind throughout the world

'What I have collected and presented, has required more labor than many of our brethren might suppose; and yet, they will not, perhaps, realize so fully as I do myself, how much must be added, how many errors corrected, before the pages through which they have travelled, can be entitled to universal acceptance.'

DANIEL DRAKE, 1850–4

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